would simplify drug product labels and reduce the possibility of medication errors.

FDA's legal authority to amend its regulations governing the content and format of labeling for human prescription drug and biologic products and to amend its regulations governing the requirements for prescription drug product labels derives from sections 201, 301, 501, 502, 503, 505, and 701 of the act (21 U.S.C. 321, 331, 351, 352, 353, 355, and 371) and section 351 of the PHS Act (42 U.S.C. 262).

A. Summary of Provisions in Proposed Rule That Contain Collections of Information

1. Requirements on Content and Format of Labeling for Human Prescription Drugs and Biologics (Proposed § 201.56)

Current FDA regulations at § 201.56 require that prescription drug labeling contain certain information in the format specified in current § 201.57. Current § 201.56 also sets forth general requirements for prescription drug labeling, including the requirement that labeling contain a summary of the essential scientific information needed for the safe and effective use of the drug, that it be informative and accurate without being promotional in tone or false or misleading, and that labeling be based whenever possible on data derived from human experience. In addition, current § 201.56 sets forth required and optional section headings for prescription drug

labeling and specifies the order in which those headings must appear.

The proposal would revise current § 201.56 to set forth: (1) General labeling requirements applicable to all prescription drugs; (2) the categories of new and more recently approved prescription drugs subject to the revised content and format requirements in proposed §§ 201.56(d) and 201.57; (3) the schedule for implementing the revised content and format requirements in proposed §§ 201.56(d) and 201.57; (4) the required and optional sections and subsections associated with the revised format in proposed § 201.57; and (5) the required and optional sections and subsections for the labeling of older prescription drugs not subject to the revised format and content requirements.

2. Specific Requirements on Content and Format (Proposed § 201.57)

Current § 201.57 specifies the kind of information that is required to appear under each of the section headings set forth in § 201.56. This information is intended to help ensure that health care practitioners are provided with a complete and accurate explanation of prescription drugs to facilitate safe and effective prescribing. Thus, current FDA regulations already require prescription drug labeling to contain detailed information on various topics that may be important to practitioners.

The proposed regulations would require that prescription drug labeling for newer products include a new section entitled "Highlights of Prescribing Information" (proposed § 201.57(a)) and a new section containing an index to prescribing information (entitled "Comprehensive Prescribing Information: Index"; proposed § 201.57(b)). The proposal would also reorder currently required information (current § 201.57, proposed as § 201.57(c) "Comprehensive Prescribing Information"), make minor content changes, and establish minimum graphical requirements.

Proposed § 201.57(a) would require that the labeling of newer human prescription drugs contain a new section entitled "Highlights of Prescribing Information." Information under this section would be a concise extract of the most important information already required under current § 201.57, as well as certain additional information that the agency believes is important to prescribers.

Proposed § 201.57(b) would require that the labeling of newer human prescription drugs contain a new section entitled "Comprehensive Prescribing Information: Index" and would consist of a list of all the sections of the labeling required in the Comprehensive Prescribing Information (proposed § 201.57(c); current § 201.57), preceded by a corresponding index number or identifier.

Proposed § 201.57(c) would require that the labeling of newer human prescription drugs contain a section entitled

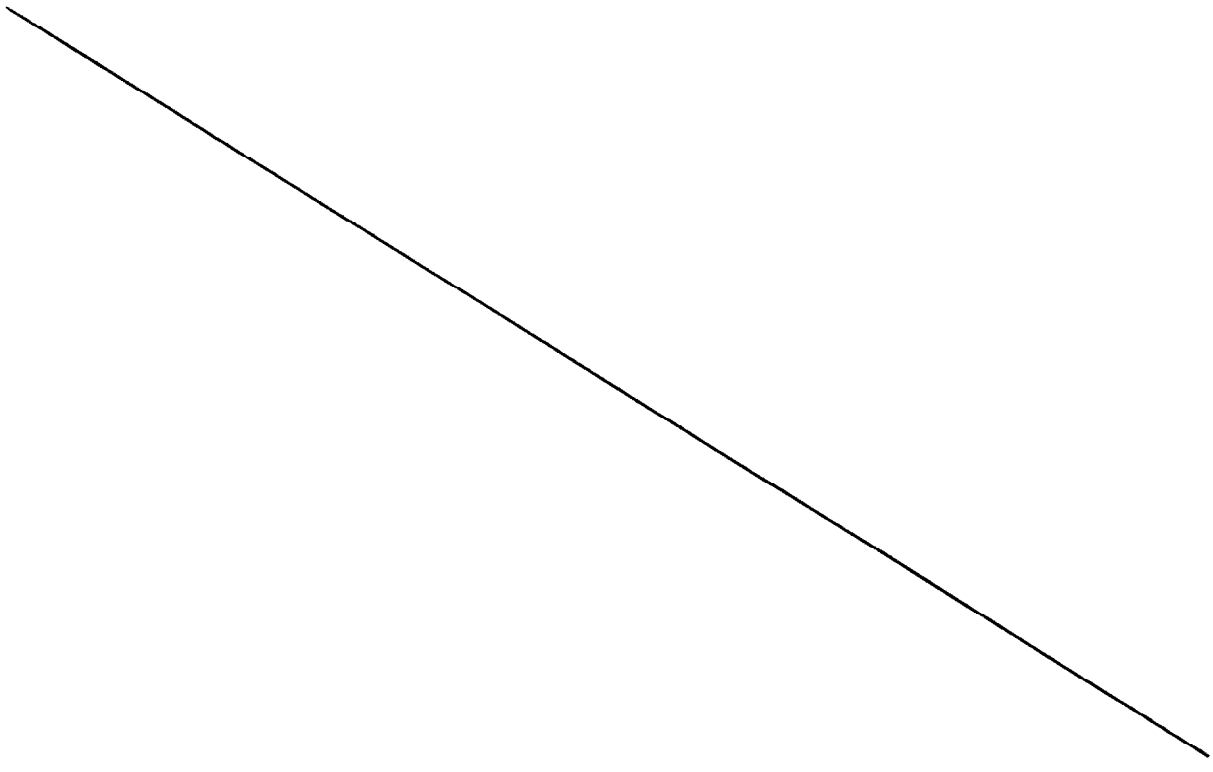
"Comprehensive Prescribing Information" and would revise the content and format of the labeling requirements contained in current § 201.57 to make it easier for health care practitioners to access, read, and use the labeling information. The proposal would reorder the information to place more prominently those sections found to be most important and most commonly referenced by practitioners. In most cases, this would require moving the information closer to the beginning of the comprehensive section. The proposal would also reorganize sections of the labeling, require standardized index numbers for each subheading, and make certain other format and content changes.

Although current §§ 201.56 and 201.57 set forth required headings and a required order for prescription drug labeling information, they do not contain requirements for a minimum type size or other graphical elements. Proposed § 201.57(d) would set forth new minimum requirements for the format of prescription drug labeling to improve its legibility, readability, and usability. The proposal would establish minimum requirements for key graphic elements such as bold type, bullet points, type size, spacing, and other highlighting techniques.

Older drugs not subject to the revised labeling content and format requirements in proposed § 201.57 would remain subject to the requirements in current § 201.57 which would be redesignated as § 201.80. In addition to the redesignation of current § 201.57, the proposed rule would make certain revisions to its

content. The content revisions being proposed are consistent with certain revisions for newer drugs in proposed § 201.57. These revisions are designed to help ensure that labeling statements related to effectiveness or dosage and administration are sufficiently supported.

In addition to revising the regulations governing the format and content of labeling for prescription drugs, proposed § 201.100(b) would make minor revisions to the information required to appear on prescription drug product labels. The proposed changes are intended to lessen overcrowding of drug product labels by eliminating unnecessary statements and moving to the package insert less critical information that currently must appear on the product label.



B. Estimates of Reporting Burden

1. Labeling Design, Testing, and Submission to FDA for New Applications (§§ 201.56 and 201.57)

Current § 201.56 requires that prescription drug labeling contain certain information in the format specified in current § 201.57, and also sets forth general requirements for prescription drug labeling. Current § 201.57 specifies the kind of information that is required to appear under each of the section headings set forth in § 201.56. As a result of these regulations, applicants must design drug product labeling, test the designed labeling, and prepare and submit the labeling to FDA for approval. Based on information received from the pharmaceutical industry, FDA estimates that it takes applicants approximately 3,200 hours to design, test (e.g., to ensure that the redesigned labeling will still fit into carton-enclosed products), and submit prescription drug product labeling to FDA as part of a new drug application. Annually, FDA receives (on average) 137 new applications containing such labeling from approximately 101 applicants.

2. The Reporting Burdens for the General Requirements (Proposed § 201.56)

The reporting burdens for the general requirements in proposed § 201.56(a) are the same as those for current § 201.56(a) through (c), and are estimated in table 2 under current §§ 201.56 and 201.57. Proposed § 201.56(b) and (c) set

forth the categories of new and more recently approved prescription drugs subject to the revised content and format requirements in proposed §§ 201.56(d) and 201.57 and the schedule for implementing the revised content and format requirements. No reporting burdens are directly associated with these requirements. Proposed § 201.56(d) sets forth the required and optional sections and subsections associated with the revised format in proposed § 201.57. The reporting burdens for this paragraph are estimated in table 2 under the requirements for proposed § 201.57.

Proposed §§ 201.56(e) and 201.80 set forth the labeling requirements for older prescription drugs. These are the same as the requirements in current §§ 201.56 and 201.57, with one exception. The exception is that provisions have been added in proposed § 201.80(b), (c), (f), (j), and (m) that would require certain statements to be removed from labeling or modified within 1 year of the effective date of the final rule. Therefore, the reporting burden associated with proposed §§ 201.56(e) and 201.80 will generally be the same as that for current §§ 201.56 and 201.57, which has been estimated in table 2. The reporting burden for proposed § 201.80(b), (c), (f), (j), and (m) is estimated in table 2 under proposed § 201.80, and has been combined with the reporting burden for the corresponding requirements for newer drugs in proposed § 201.57(c).

3. Labeling Redesign, Testing, and Submission to FDA for Approved Applications (Proposed § 201.57(a), (b), (c), and (d))

Proposed § 201.57(a) would require a new section in prescription drug product labeling entitled "Highlights of Prescribing Information"; proposed § 201.57(b) would require a new section in the labeling entitled "Comprehensive Prescribing Information: Index"; proposed § 201.57(c) would require a revision of the content and format requirements in current § 201.57 and a new title "Comprehensive Prescribing Information"; and proposed § 201.57(d) would establish new requirements for type size and other graphical elements. For applications approved during the 5 years before the effective date of these new prescription drug labeling requirements, and for applications pending on the effective date, applicants must redesign drug product labeling, test the redesigned labeling (e.g., to ensure that the larger labeling will still fit in carton-enclosed products), and prepare and submit that labeling to FDA for approval. Based on the data and information provided in the "Analysis of Economic Impacts" (section X of this document), approximately 366 labeling supplements would be submitted to FDA during the period 3 to 7 years after the effective date. Approximately 145 applicants would submit these labeling supplements, and the time required for redesigning, testing, and submitting the labeling to FDA would be approximately 190 hours.

4. Labeling Revision and Submission to FDA Within 1 Year for Approved Applications (Proposed § 201.57(c) and Proposed § 201.80(b), (c), (f), (j), and (m))

Under the "Proposed Implementation Plan" (see section IV of this document), certain provisions under proposed § 201.57(c) and proposed § 201.80 would be implemented within 1 year after the effective date. Based on the data and information provided in the analysis of economic impacts, approximately 1,888 labeling supplements would be submitted to FDA during the first year after the effective date. Approximately 145 applicants would submit these labeling supplements, and the time required for revising and submitting the labeling for these supplements would be approximately 38 hours.

5. Labeling Design and Testing for New Applications (Proposed § 201.57(a), (b), (c), and (d))

Under the proposed implementation plan, prescription drug labeling in new applications submitted after the effective date must include new sections entitled "Highlights of Prescribing Information" and "Comprehensive Prescribing Information: Index," as well as other new information and features not currently required in prescription drug labeling. Based on the data and information provided in the economic analysis, approximately 1,421 new applications would be submitted to FDA over a 10-year period after the effective date. Approximately 145 applicants would submit these applications, and the time required for the

new labeling design and testing for each application would be approximately 149 hours.

6. Label Revisions (Proposed § 201.100(b))

In addition to revising the regulations governing the format and content of labeling for prescription drugs, the proposal, as explained above, would make minor revisions to the information required to appear on prescription drug product container labels. Neither the economic analysis nor this Paper Reduction Act analysis include burden estimates for these label revisions because, under the proposed rule, these changes do not have to be made until the next label revision. Thus, no new burdens would result from these proposed label revisions.

C. Capital Costs

A small number of carton-enclosed products may require new packaging to accommodate the longer insert. The economic analysis estimates that 1 percent of both the products with new efficacy supplement changes and the products approved in the 5 years before the effective date of the rule would incur costs of $200,000 each for needed packaging changes. Products approved after the effective date of the final rule would not incur added equipment costs because their labeling and packaging are not yet

established. The estimated present costs for equipment changes over 10 years totals $1 million.

Description of Respondents: Persons and businesses, including small businesses and manufacturers.

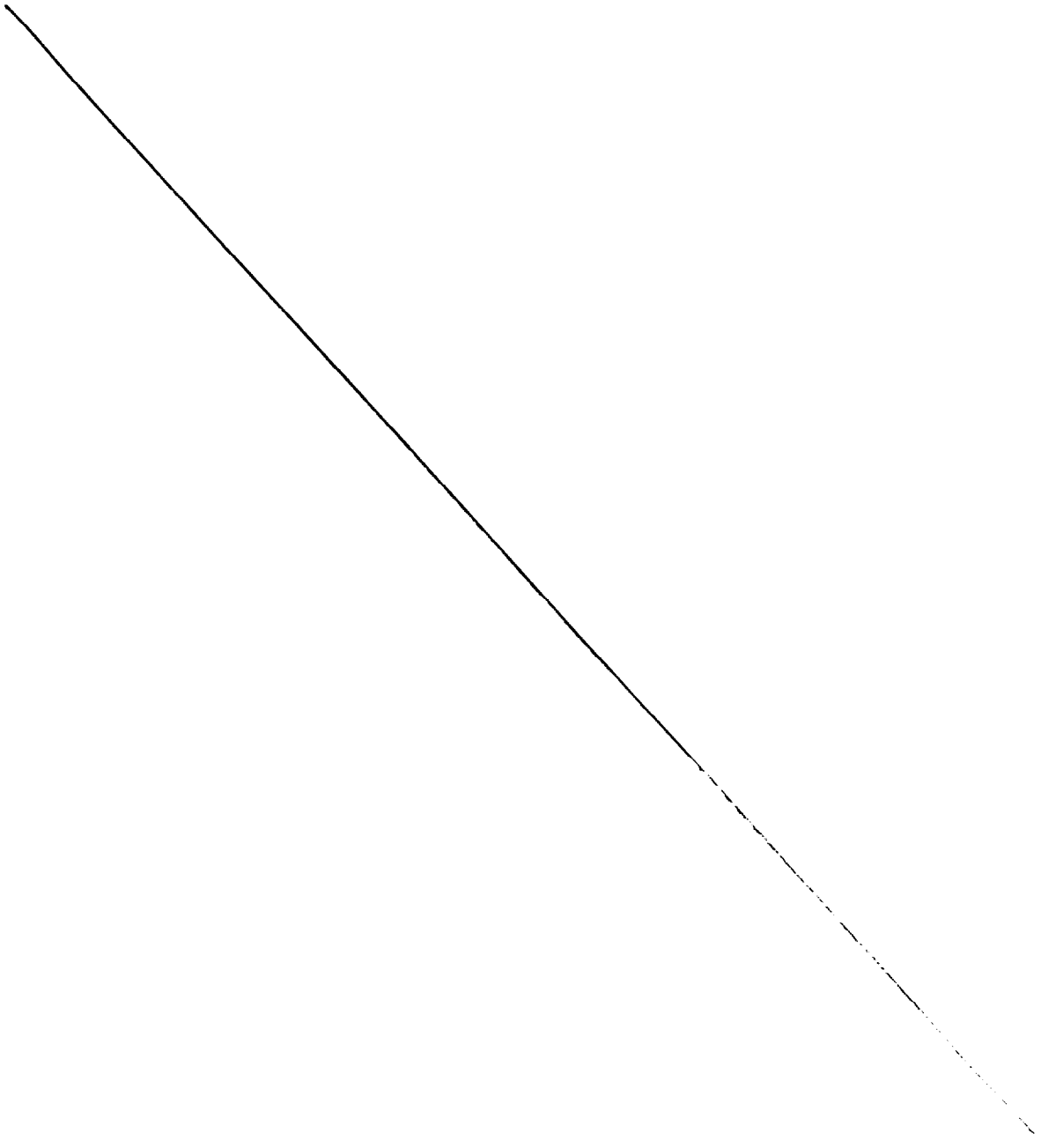


Table 2.--Estimated Reporting Burden[1]

21 CFR Section	Number of Respondents	Number of Responses per Respondent	Total Responses	Hours per Response	Total Hours
Current 201.56 and 201.57 Labeling design, testing, and submission to FDA for new applications.	101	1.36	137	3,200	438,400
Proposed 201.57(a), (b), (c), (d) Labeling redesign, testing, and submission to FDA for approved applications.	145	2.52	366	190	69,540
Proposed 201.57(c) and 201.80 Labeling revision and submission to FDA within 1 year for approved applications.	145	13.02	1,888	38	71,744
Proposed 201.57(a), (b), (c), (d) Labeling design and testing for new applications.	145	9.80	1,421	149	211,729
Total					791,413

[1]There is no capital costs or operating and maintenance costs associated with this collection of information.

In compliance with the Paperwork Reduction Act of 1995(44 U.S.C. 3507)d)), the agency has submitted the information collection provisions of this proposed rule to OMB for review. Interested persons are requested to send comments regarding collection of information by [insert date 30 days after date of publication in the FEDERAL REGISTER], to the Office of Information and Regulatory Affairs, OMB, New Executive Office Bldg., 725 17th St. NW., rm. 10235, Washington, DC 20503, Attn: Wendy Taylor.

VIII. Environmental Impact

The agency has determined under 21 CFR 25.30(h) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

IX. Executive Order 13132: Federalism

FDA has analyzed this proposed rule in accordance with Executive Order 13132: Federalism. The Order requires Federal agencies to carefully examine actions to determine if they contain policies that have federalism implications or that preempt State law. As defined in the Order, "policies that have

federalism implications" refers to regulations, legislative comments or proposed legislation, and other policy statements or actions that have substantial direct effects on the States, on the relationship between the National Government and the States, or on the distribution of power and responsibilities among the various levels of government.

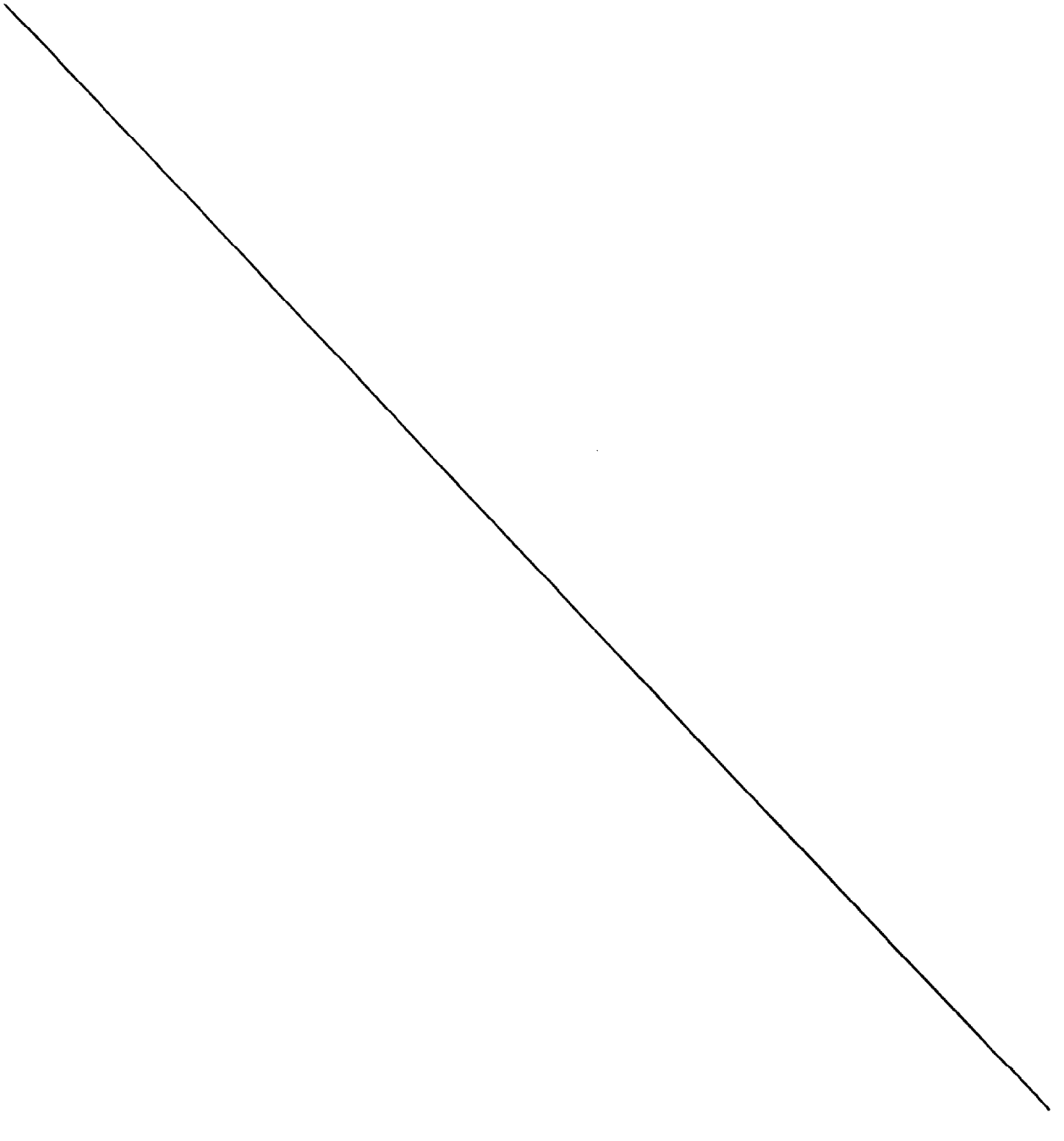
FDA is publishing this proposed rule to revise its regulations governing the format and content of labeling for human prescription drug products. The proposal would revise current regulations to require that labeling include a section containing highlights of prescribing information and a section containing an index to prescribing information. The proposal would also reorder currently required labeling information and make minor changes to its content. Finally, the proposal would establish minimum graphical requirements for labeling. This proposal would also eliminate certain unnecessary statements on prescription drug product labels and move other, less important information to labeling. Because enforcement of these labeling provisions is a Federal responsibility, there should be little, if any, impact from this rule, if finalized, on the States, on the relationship between the National Government and the States, or on the distribution of power and responsibilities among the various levels of Government. In addition, this proposed rule does not preempt State law.

Accordingly, FDA has determined that this proposed rule does not contain policies that have federalism implications or that preempt State law.

X. Analysis of Economic Impacts

FDA has examined the impacts of the proposed rule under Executive Order 12866, the Regulatory Flexibility Act (5 U.S.C. 601-612), and the Unfunded Mandates Reform Act (Public Law 104-4). Executive Order 12866 directs agencies to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and equity). Under the Regulatory Flexibility Act, if a rule may have a significant economic impact on a substantial number of small entities, an agency must consider alternatives that would minimize the economic impact of the rule on small entities. Section 202(a) of the Unfunded Mandates Reform Act of 1995 (Public Law 104-4) requires that agencies prepare a written assessment of anticipated costs and benefits before proposing any rule that may result in an expenditure by State, local, and tribal governments, in the aggregate, or by the private sector of $100 million in any one year (adjusted annually for inflation).

The agency believes that this proposed rule is consistent with the regulatory philosophy and principles identified in Executive Order 12866 and in these two statutes. The proposed rule would amend current requirements for the format and content of labeling for human prescription drug and biologic products.



Based on the analysis following, as summarized in table 3, FDA projects that the present value of the quantifiable benefits of the proposed rule could exceed $296 million over 10 years. Direct costs resulting from the proposed changes are projected to range from approximately $8 million to $16.9 million in any one year, for a total present value of approximately $94.5 million over 10 years at 7 percent. The agency thus concludes that the benefits of this proposal substantially outweigh the costs. Furthermore, the agency has determined that the proposed rule is not an economically significant rule as described in the Executive Order, because annual impacts on the economy are substantially below $100 million.

The Unfunded Mandates Reform Act does not require FDA to prepare a statement of costs and benefits for the proposed rule because the proposed rule is not expected to result in any one-year expenditure that would exceed $100 million adjusted annually for inflation. The current inflation-adjusted statutory threshold is $110 million.

This rule may affect a substantial number of small entities, as defined by the Regulatory Flexibility Act. About half of the costs associated with relabeling are directly proportional to sales volume; thus, products with fewer sales would be associated with relatively lower relabeling costs. Nonetheless, it is possible that some small firms that produce small amounts of affected drugs, or small firms that might be required to

undertake packaging modifications, may be significantly affected by this proposed rule. The following analysis constitutes the agency's initial regulatory flexibility analysis as required by the Regulatory Flexibility Act.

Table 3.--Summary of Projected Quantifiable Benefits and Costs Over 10 Years

Benefits and Costs	Total ($million)	Present Value ($million)
Benefits:		
Physician time saved	102.09	62.76
Adverse drug events avoided	345.58	233.80
Total Benefits	447.67	296.56
Costs:		
Reformatting, revising, and FDA approval	14.68	11.62
Producing prescription drug labeling	81.43	54.37
PDR costs	43.96	28.54
Total Costs	140.07	94.53

A. Purpose

The objective of the proposed rule is to make it easier for health care practitioners to find, read, and use information important to the safe and effective prescribing of prescription pharmaceuticals (drugs and biologics) for patient treatment. The agency has found that the current format, while effective, can be

improved to more optimally communicate important drug information. The proposed rule is designed to achieve this objective by amending the current format for the labeling of human prescription drug and biological products to, among other things, highlight frequently accessed and new information, include an indexing system, and reorder certain information.

B. Benefits of Regulation

The expected economic benefits of this proposed rule are the sum of the present values of: (1) The reduced time needed by health professionals to read or review prescription drug labeling for desired information; (2) the increased effectiveness of treatment; and (3) the decreased number of adverse events resulting from avoidable drug-related errors.

1. Decreased Health Professional Time

The proposed new format for prescription drug labeling (i.e., package inserts or professional labeling) would reduce the time physicians, pharmacists, and other health professionals must spend reading prescription drug labeling by highlighting frequently used information, by including an indexing system to direct readers to more detailed material in other sections of the labeling, and by reordering and reorganizing the detailed material to facilitate access to information deemed to be most important to prescribers. Although FDA is unaware of any data

estimating the total time health professionals spend reading the labeling of prescription drugs, a 1994 FDA survey of physicians found that 42 percent referred to labeling at least once a day, 33 percent less often than once a day but more often than once a week, and 25 percent once a week or less. Even if physicians spend, on average, only 30 seconds referring to labeling (once the labeling is at hand), these findings imply that the cumulative amount of time spent referring to labeling by the nation's approximately 599,000 physicians active in patient care equals about 1.1 million hours per year (Ref. 14). If the new format reduced by 15 seconds the amount of time physicians needed to find information on prescription drug labeling, implementing that format for all prescription drug products would save approximately 525,000 hours per year.

Although the proposed rule initially applies to only a small percentage of all prescription drug labeling, its focus on the most recently approved products includes the labeling that health professionals are most likely to consult frequently. In FDA's survey of physicians, newness of the product was the factor most often rated by physicians as "very likely" to trigger referral to prescription drug labeling. This analysis assumes that the rule will begin affecting labeling consultations in the second year of implementation and that it will affect 5 percent of all consultations in that year. The percentage of reformatted labeling consulted by physicians is assumed to increase to 10,

Table 4.--Annual Benefits of Regulation

Year	Physician Time Saved ($ million)		Adverse Drug Events Avoided ($ million)		Total Benefits ($ million)	
	Current Value	Present Value	Current Value	Present Value	Current Value	Present Value
1	$0.00	$0.00	$0.00	$0.00	$0.00	$0.00
2	$2.00	$1.75	$38.40	$33.54	$40.40	$35.29
3	$4.00	$3.27	$38.40	$31.34	$42.40	$34.61
4	$6.01	$4.58	$38.40	$29.29	$44.40	$33.87
5	$10.01	$7.14	$38.40	$27.38	$48.41	$34.51
6	$12.01	$8.00	$38.40	$25.59	$50.41	$33.59
7	$14.01	$8.73	$38.40	$23.91	$52.41	$32.64
8	$16.01	$9.32	$38.40	$22.35	$54.41	$31.67
9	$18.02	$9.80	$38.40	$20.89	$56.41	$30.69
10	$20.02	$10.18	$38.40	$19.52	$58.41	$29.70
Total	$102.09	$62.76	$345.60	$233.81	$447.66	$296.57

2. Improved Effectiveness of Treatment

Under the proposed rule, the highlights section would emphasize the drug information that physicians report is the most important for decisionmaking. In addition, any patient information or Medication Guide approved by FDA would be printed at the end of the labeling regardless of when the product was approved. Moreover, certain information will be removed from existing professional labeling because the rule only allows inclusion of data that are pertinent to the clinical uses specified in the indications section. Consequently, this proposed rule would improve the ability of physicians to select the most safe and effective pharmaceutical treatments for their patients and to administer those treatments in the most safe and

effective manner. In addition, the proposal may enhance the likelihood that physicians will communicate important information to patients, which could improve patient understanding and compliance with treatment. FDA is unable to quantify the magnitude of these expected improvements in treatment effectiveness and health outcomes, but the agency believes they could be significant.

3. Decrease in Avoidable Adverse Events

Because it will highlight important information about dosage, side effects, and contraindications, the proposed new prescription drug labeling format would decrease the number of adverse drug events (ADE's) caused by incorrect product use. Many ADE's result from poor or incorrectly applied information (e.g., prescribing too high a dose for a patient with poor kidney function, or prescribing a drug to a patient with known contraindications) and are potentially preventable. Studies of hospitalized patients in the early 1990's suggest that the rate of preventable ADE's that occur during hospitalization is approximately 1.2 to 1.8 ADE's per 100 patients admitted (Refs. 15 and 16). Moreover, the latter study found that a majority of preventable ADE's (about 1 ADE per 100 hospital admissions) were related to errors or miscalculations in physician ordering, the stage most likely to be affected by improved prescription drug labeling information. Given the approximately 35 million

hospitalizations annually in the United States,[13] these data suggest that about 350,000 ADE's among hospitalized patients are potentially preventable with better labeling for health professionals. Studies show that the occurrence of an ADE in a hospitalized patient increased the costs of caring for the patient by an average of $2,262 to $2,595 (Refs. 15 and 17). Costs associated with preventable ADE's were even higher, averaging about $4,685 per patient (Ref. 17). If other hospitals incur similar costs for preventable ADE's, the potentially preventable annual costs from this source could total $1.6 billion nationally.

In addition, many outpatients are hospitalized as a result of preventable adverse events associated with outpatient drugs. FDA previously estimated that the costs associated with these hospitalizations total $4.4 billion per year[14] (60 FR 44232,

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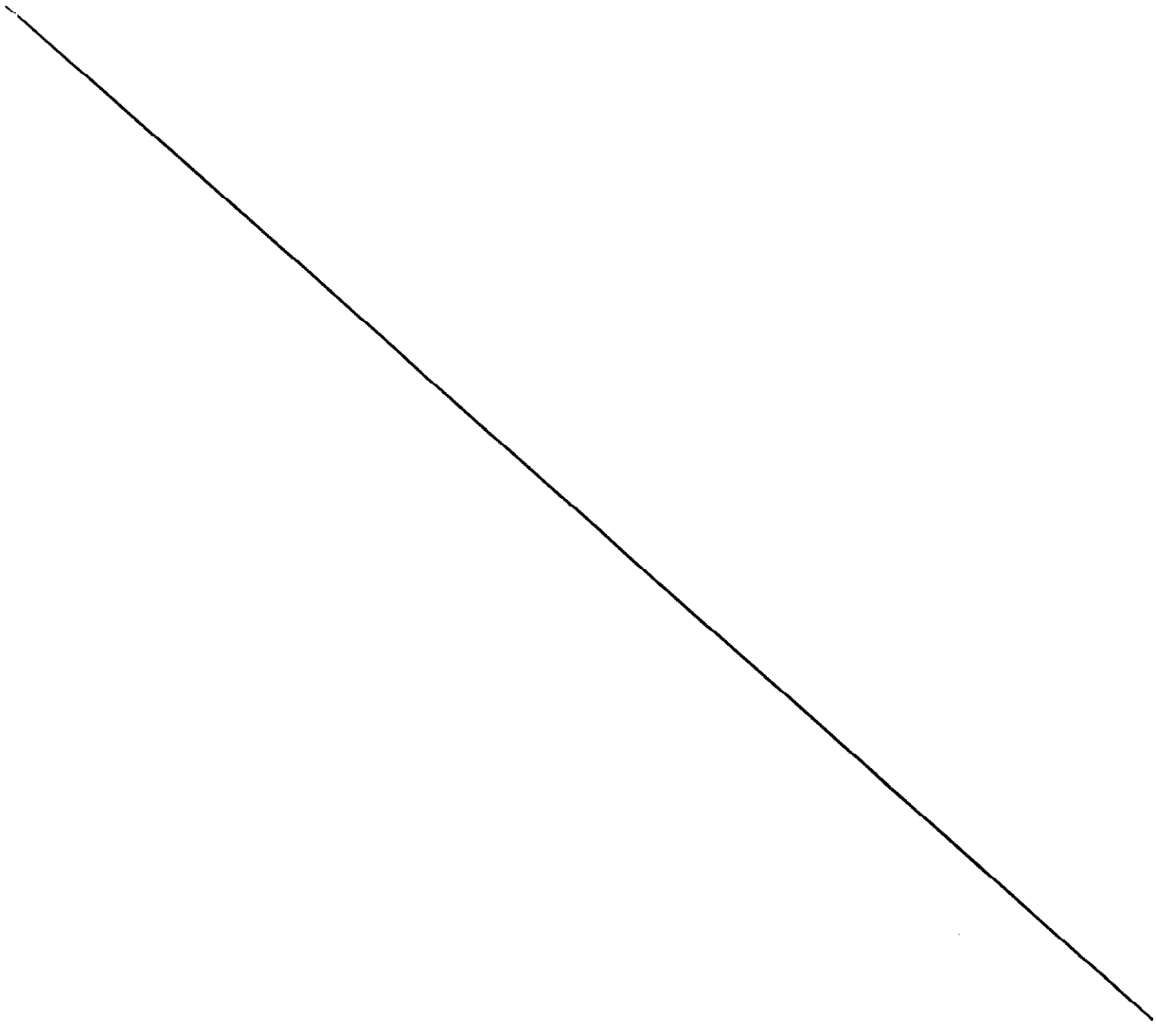
[13]1997 hospital discharges, Heathcare Cost and Utilization Project (HCUP) Nationwide Inpatient Sample, 1997, Agency for Healthcare Research and Quality (AHRQ), April 2000. Http://www.ahrq.gov/data/hcupnet.htm.

[14]60 FR 44232, August 24, 1995. An estimated 498,750 patients are hospitalized annually for a preventable adverse drug reaction to a prescription drug product, costing $4.4 billion in hospital charges. ($4.4 billion = 498,750 patients x $8,890 average hospital charges per patient; 498,740 patients = 35 million discharges x 3% treated for adverse drug events x 95% of adverse drug events from prescription drug products x 50% of adverse drug events that are preventable.)

August 24, 1995). If half of these adverse events also are related to physician ordering errors, about $2.2 billion per year additional hospital costs result from this source of error. Thus, combining both inpatient and outpatient adverse drug events, about $3.8 billion per year in hospital costs may be potentially preventable through better prescription drug labeling.



The actual proportion of the ADE costs that would be prevented under the proposed rule cannot be predicted with certainty. If these costs were reduced by even 1 percent, however, the proposed rule would reduce hospitalization costs by $38.4 million per year. Over 10 years, the present value of these benefits would total $233.8 million (table 4). Furthermore, if additional averted costs (e.g., physician visits, additional outpatient costs, patient time, lost productivity) were included, the savings from the ADE's avoided would be substantially higher.

C. Costs of Regulation

The proposed rule mandates two broad types of changes to the labeling of prescription drug products. First, the professional labeling of recently approved and future products must follow format and content requirements proposed in the rule. Second, some labeling of products already approved for marketing must be revised to: (1) Delete information not pertinent to the approved indication, and (2) add previously approved printed patient information or a Medication Guide. Therefore, direct costs incurred to change professional labeling include the costs of: (1) Designing or revising prescription drug labeling and submitting the new labeling to FDA for approval, (2) the costs of producing longer labeling, and (3) printing a longer PDR.

1. Labeling Changes for Recently Approved and Future Prescription Drug Products

a. Affected products. The proposed rule would require that prescription drug labeling conform to format and content requirements for two categories of products: (1) All NDA's, BLA's, and efficacy supplements submitted to FDA on or after the effective date of the final rule: and (2) all NDA's, BLA's, and efficacy supplements pending at the time of the effective date of the final rule or approved over the 5 years preceding the effective date of the final rule. For the first category of products, the labeling requirements would apply when a sponsor files an NDA or BLA (new applications) or efficacy supplement. Products in the second category must file supplemental applications within 3 to 7 years after the effective date of the final rule according to the implementation plan provided in table 1. Labeling for nonprescription products (including nonprescription products approved under NDA's) is not covered by this rule.

Estimates of the number of new applications that would be affected by the rule over a 10-year period are shown in table 5 and are based on the number of application approvals since 1990.

Table 5.--Number of Affected New Drug and Biological Applications and Estimated Labeling Design Costs

Year	Number of Affected Applications by Type				Cost for Prescription Drug Labeling Design ($ mil)				
	New NDA's/ BLA's	ES's*	Before-5**	Total	New NDA's/ BLA's	ES's*	Before-5**	Total	Present Value
1	85	59	0	144	$0.43	$0.30	$0.00	$0.72	$0.67
2	134	73	0	207	$0.67	$0.37	$0.00	$1.04	$0.90
3	121	57	74	252	$0.61	$0.29	$0.56	$1.45	$1.18
4	113	38	74	225	$0.57	$0.19	$0.56	$1.31	$1.00
5	113	20	73	206	$0.57	$0.10	$0.55	$1.21	$0.86
6	113	14	73	200	$0.57	$0.07	$0.55	$1.18	$0.79
7	113	10	72	195	$0.57	$0.05	$0.54	$1.16	$0.72
8	113	8	0	121	$0.57	$0.04	$0.00	$0.61	$0.35
9	113	6	0	119	$0.57	$0.03	$0.00	$0.60	$0.32
10	113	5	0	118	$0.57	$0.03	$0.00	$0.59	$0.30
Total	1,131	290	366	1,787	$5.66	$1.47	$2.76	$9.87	$7.09

* Efficacy supplements

** Approvals 5 years before effective date.

For this analysis, January 1, 1995, was used as a proxy for the effective date of the proposed rule. The number of covered application approvals for the 3 consecutive years beginning in 1995 were 85, 134, and 121, an average of 113 each year. FDA assumes that this average rate will continue. During this same 3-year period, 59, 73, and 57 efficacy supplements were approved for applications that initially had been approved prior to 1995. FDA estimates, therefore, that if this rule had become effective on January 1, 1995, as many as 144 products (i.e., 85 covered applications and 59 efficacy supplements) would have incurred design costs in the first year. Most efficacy supplements are filed and approved within 5 years of the approval date of their original application. Therefore, beginning in 1997, an increasing number of efficacy supplements would not have required changes to the labeling format because these changes would have been made in the original application. As the annual number of affected efficacy supplements declined over time, the annual number of affected total applications would likewise diminish, as projected in table 5. Furthermore, between 1990 and 1994 (i.e., the 5-year period before the proxy effective date), an additional 366 applications were approved. Thus, an average of 73 additional applications would have been received annually in years 3 through 7.

b. Prescription drug labeling design costs. The cost of designing prescription drug labeling that conforms to the proposed format and content requirements will depend heavily on when, during a product's life cycle, labeling design occurs. Costs will be highest for products already marketed with approved labeling that would otherwise not be changed. Conversely, design costs will be lowest for products that are closely related to a prior product application that has already had its labeling changed to the new format. Costs for currently marketed products undergoing relabeling for other reasons (e.g., related to an efficacy supplement) will be intermediate between these extremes.

FDA has estimated the cost of designing novel patient labeling (for the first prescription drug in a therapeutic class) at about $12,000.[15] The estimated costs of redesigning patient labeling for products that could use previously developed prototypes (i.e., generic drugs or innovator drugs in the same therapeutic class for which patient labeling was already developed) ranged from $500 to $1,500 per product. Although the design of prescription drug labeling under the proposed rule will primarily follow a format specified by FDA, detailed discussion and drug-specific decisions (e.g., regarding exactly which

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[15]60 FR 44232. $11,667 for 2 months full-time effort of professional/technical employees with annual compensation, including 40 percent benefits of $70,000 ($11,667 = $50,000 x 1.4 x 2/12).

adverse reactions should be listed in the highlights section) will be necessary. Consequently, this analysis estimates $7,500 as the average cost to a firm that needs to redesign the labeling of an existing innovator drug, to test the redesigned labeling (e.g., to ensure that the larger labeling will still fit in carton-enclosed products), and to prepare and submit that labeling to FDA for approval. Additional costs for the latter task, however, would be incurred only for those drugs approved in the 5 years before the effective date of the rule. Although sponsors of new applications and efficacy supplements would incur many of the same design costs, they would experience no additional testing and application costs. Thus, the design of labels for new applications and efficacy supplements is estimated to cost $5,000 on average.

In the first year after the final rule becomes effective, an estimated 144 affected products would incur an additional cost per drug of $5,000 to comply with the proposed rule. As shown in table 5, the total first-year costs would amount to $720,000, increasing in the second year to $1.04 million. Costs increase in year 3 to a high of $1.45 million as sponsors of recently approved products begin submitting FDA supplemental applications, at $7,500 per application, to comply with the new labeling format and content. After the seventh year, when all products approved within 5 years before the rule's effective date or pending approval at that time have redesigned labeling, the costs decline

to about $0.6 million per year. As a result, the estimated present value of the costs of redesigning prescription drug labeling over 10 years is about $7.1 million.

c. Costs associated with producing labeling. Under the proposed rule, labeling for each affected product would be expanded to include a highlights section, an index, and additional formatting and font size requirements (if the labeling does not already meet these requirements). Consequently, all affected labeling will be longer than at present, with current shorter labeling affected proportionately more than current longer labeling (due to the fact that the highlights section will add nearly the same amount of absolute length to every affected product with prescription drug labeling). Longer labeling increases the cost of paper, ink, and other ongoing incremental printing costs. These costs apply both to the labeling that physically accompanies the product and to the labeling that accompanies promotional materials. Also, some products packaged in cartons containing package inserts will require a product-by-product review to assess whether the carton can still accommodate the longer labeling. It is possible that a few products would require equipment changes (e.g., different insert-folding machinery).

i. Incremental printing costs. Based on quotes from industry consultants, FDA estimates that the cost of printing larger prescription drug labeling is approximately $0.0086 for

each additional 100 square inches. The agency estimates that the proposed rule would increase the average size of labeling by about 93 square inches[16] adding $.008 to the per label printing cost, or $7,960 per million package inserts printed. The new highlights and index sections account for about 37 percent of the additional printing cost, whereas the larger font size imposes the remaining 63 percent of the incremental printing cost.

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[16]The length of professional labeling from a random sample of approximately 5 percent of the listings printed in the PDR averaged 2.67 pages with a font size of 6.5 point. Twenty-four percent of the sample had at least one boxed warning with an average length of about 5.6 square inches in 6.5-point font or 6.25 square inches in 8-point font. Increasing the font size from 6.5 point to 8 point (i.e., the minimum font size specified in the proposed rule) would increase the average length by an estimated 59 percent, or approximately 1.6 pages. Moreover, the agency estimates that the new highlights section, including any boxed warnings, and indexing system may add up to 90 percent of a page to professional labeling. Therefore, the proposed rule would increase the length of the average professional labeling by about 2.5 pages. Because package inserts are printed on both sides, the average package insert would increase in size by 92.6 square inches.

U.S. retail pharmacies dispense about 2.3 billion prescriptions per year, of which an estimated 560 million are for unit-of-use products, which often include labeling within the package.[17] If the remaining 1.7 billion pharmacy-prepared prescriptions average one insert per 3.33 prescriptions (assumes an average of 100 units per container and 30 units dispensed per prescription), the total number of inserts accompanying retail products equals roughly 1.1 billion. Adding hospital pharmaceutical volume, estimated at approximately 38 percent of retail volume, yields an annual total of 1.5 billion package inserts accompanying prescribed products. Allowing 10 percent for wastage indicates that pharmaceutical companies distribute roughly 1.65 billion package inserts with prescribed products each year. Over time, an increasing number of these inserts would have to be revised. Because the rule initially affects only innovator products and about 60 percent of all prescriptions are for branded products, FDA calculated that about 1 billion of these inserts are currently provided with about 2,287 branded products.[18] Thus, on average, about 435,000 inserts (1 billion ÷

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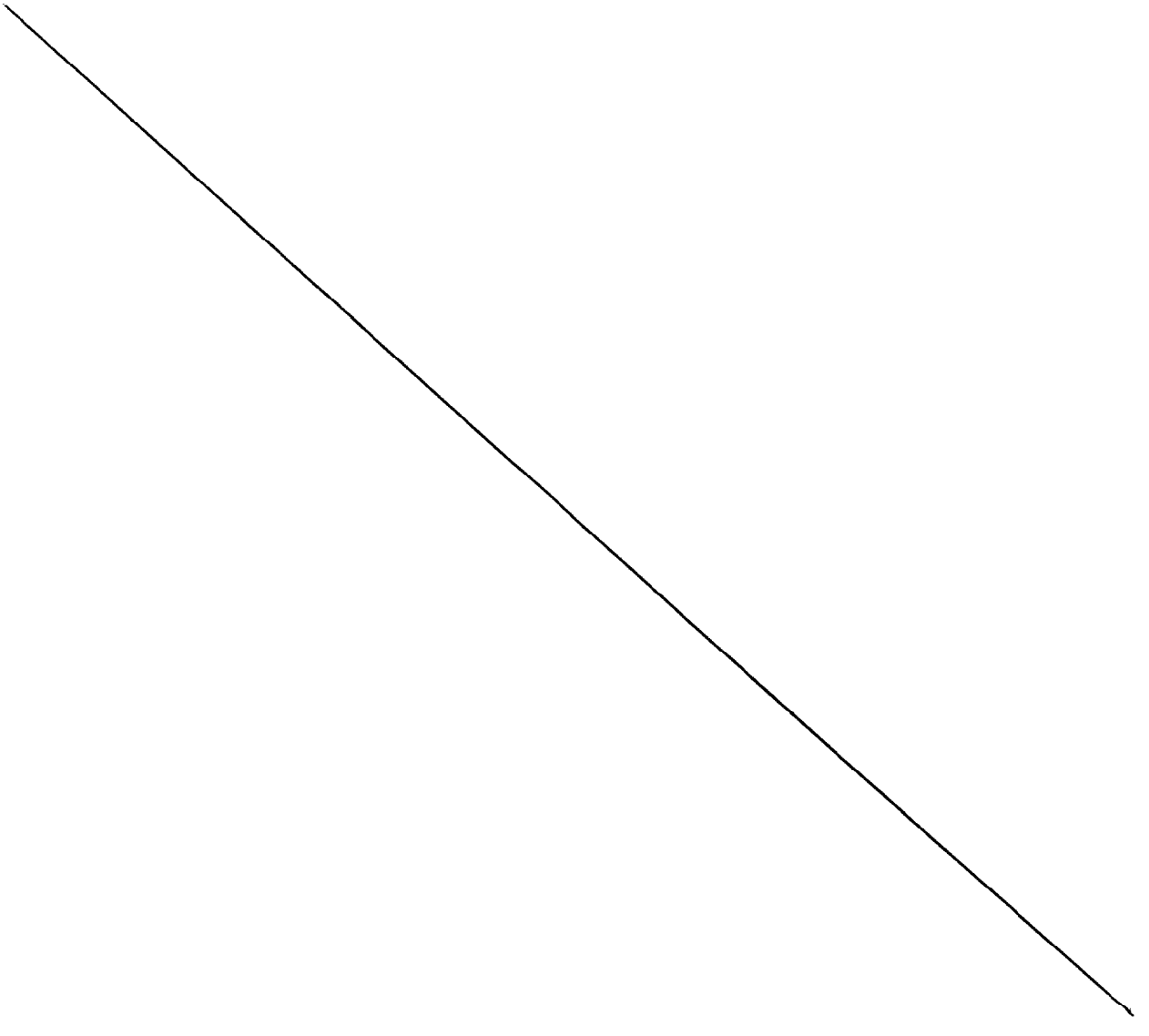
[17]Unpublished FDA analysis based on survey results from nine pharmacists and applied to IMS data.

[18]Derived from the 1998 Approved Drug Products With Therapeutic Equivalence Evaluations (Orange Book), CDER, FDA. The estimate is a count of all branded products marketed under an NDA and differentiated by active ingredient, dosage form, or manufacturer, not including multiple dosage strengths. Although biologics were not counted, adding biologics would not significantly alter results.

2,287) may be shipped annually for each affected product. Table 6 shows the estimated number of revised inserts that would accompany the prescribed products. Multiplying these numbers by the estimated incremental printing cost of $.008 per label indicates that the annual costs for package inserts would rise to about $6.2 million by the 10th year.



To calculate the amount of labeling printed for promotional purposes, FDA assumed that the 23.7 million office and hospital calls per year made by pharmaceutical representatives[19] involved an average of 2 printed pieces of labeling per visit, or a total of 47.4 million per year. In addition, sales representatives made 8.2 million sample calls, distributing an estimated 82 million package inserts per year, or an average of 10 samples per call. Since most promotional visits involve relatively new products--the products most affected by this rule--FDA assumed that all of this labeling would incur additional printing costs, amounting to about $1.0 million annually.

Finally, FDA estimated that about 800,000 pieces of labeling per approval would be distributed each year by mail or at conferences to physicians, other health care professionals, consumers, retail pharmacy outlets and hospital pharmacies for 3 years following approval of a new drug.[20] As shown in table 6,

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[19]Data from IMS, 1997, as presented at FDA on June 3, 1998. Data include an estimated 17.8 million office calls, 8.2 million sample calls, and 5.9 million hospital calls made in 1997.

[20]For each approval, it was assumed that all physicians involved in primary care and 25 percent of physicians practicing a medical specialty would receive 2 mailings per year, or an estimated 711,535 pieces (i.e., = (274,726 X 2) + (0.25 X 324,198 X 2)), for 3 years following product launch. An additional 10 percent or 71,153 pieces are estimated to be distributed annually for 3 years to other health professionals or consumers. Furthermore, FDA assumes that 50,829 retail pharmacy outlets and 7,120 hospital pharmacies would receive one mailing to announce the launch of a new product in the year of approval.

annual total promotional labeling costs peak at $5.4 million in year 4. Over 10 years, the present value of the incremental printing costs for all types of longer prescription drug labeling would be about $52.7 million.

Some companies may incur additional costs associated with maintaining the labeling posted on their web sites. The agency did not estimate these related costs but believes they would be minimal and a routine cost of doing business. Nonetheless, the agency requests comment.

ii. Equipment costs. Agency consultants with expertise in pharmaceutical labeling operations estimate that only a small number of carton-enclosed products may require new packaging to accommodate the longer insert. This analysis assumes that 1 percent of both the products with new efficacy supplement changes and the products approved in the 5 years before the effective date of the rule would incur costs of $200,000 each for needed packaging changes. Products approved subsequent to the effective date of the final rule would not incur added equipment costs because their labeling and packaging are not yet established. The estimated present value of equipment changes totals $1.0 million over 10 years.

d. PDR costs. FDA estimates that the new highlights section, including any boxed warnings, and index would add about

one-half pages to each affected labeling printed in the PDR.[21]

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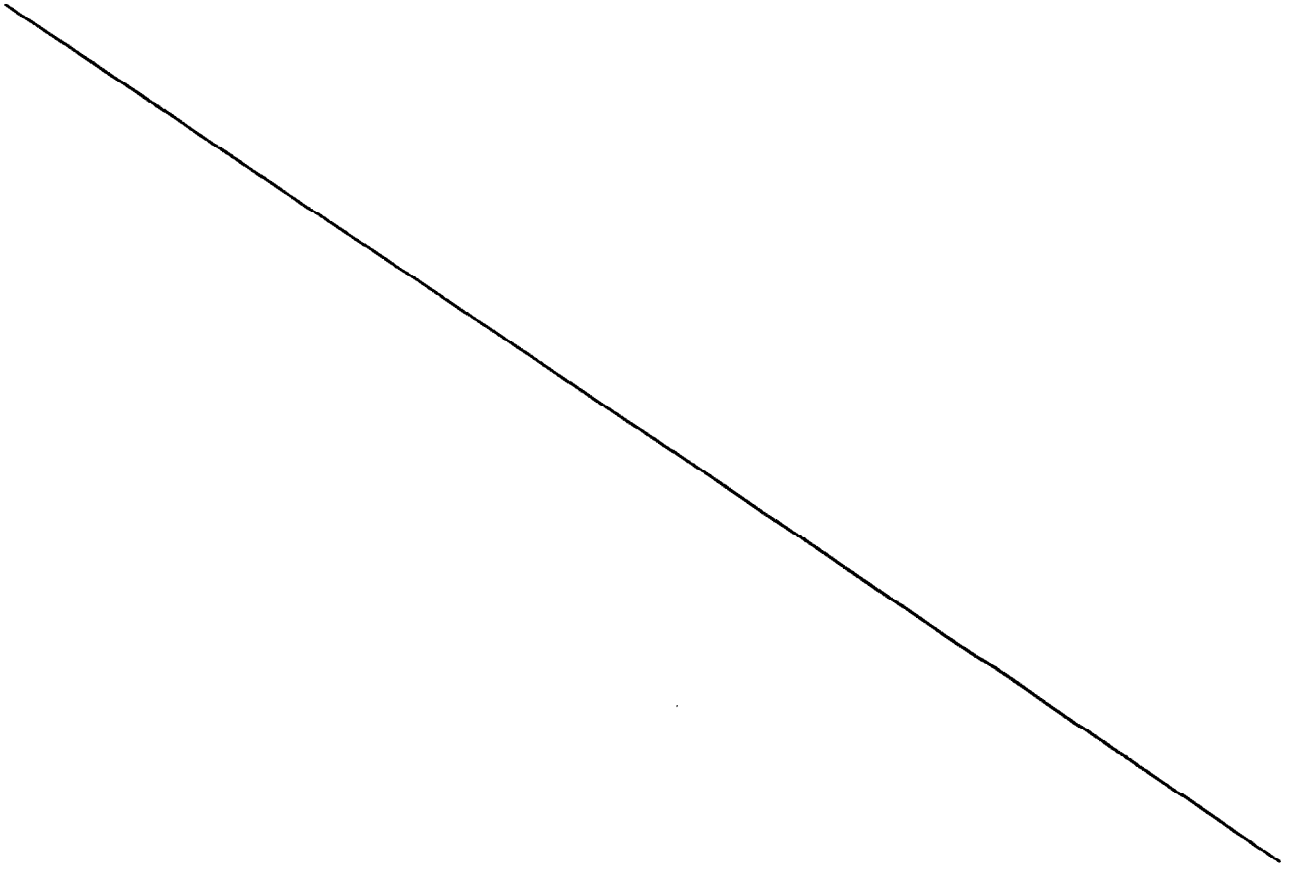
[21]The new highlights section could add up to one-half page when printed in 8-point size. Because the PDR is printed in a 6.5-point New Century Schoolbook Roman font, the highlights section would require less than one-half page in the PDR. The agency estimates 37 percent less space is required to print information in the smaller PDR font, reducing the size required for the new highlights section to 0.3 pages (i.e., 0.5 x (1 - 0.37) = 0.315 pages). A sample of labeling printed in the PDR found that about 24 percent of the products may be required to print a boxed warning averaging 5.6 square inches. Therefore, the agency estimates an additional 0.02 pages for these warnings (i.e., 23.9 percent x 5.6 square inches / 75 square inches per page = 0.02 pages). Furthermore, the new indexing system is estimated to add approximately 60 column lines to a PDR listing, equaling approximately 0.2 pages (i.e., (60 lines / 96 lines per column) / 3 columns per page = .21 pages). In total, up to .54 pages may be added to the professional labeling printed in the PDR.



Conversations with Medical Economics (the publisher of the PDR) on the cost per printed page imply that the annual publishing costs of the extra space required for printing the expanded labeling would be about $4,300 for each affected product, plus an additional cost if the product was included in one of two annual supplements. FDA assumed that these costs would be incurred by the pharmaceutical industry via publishing fees paid to Medical Economics. The agency assumed that 75 percent of the new drugs and efficacy supplements would be published in the PDR (some smaller firms decline to publish labeling in the PDR). It was further assumed that 90 percent of the new drugs published would be included in the PDR supplements and 33 percent of the published efficacy supplements would be included in the PDR supplements (about half are actually included, but only two-thirds of these include full prescription drug labeling--the remainder include only the added indication). FDA also assumed that the labeling changes made as a result of the 5-year rule (applications approved in the 5 years preceding the effective date of the final rule) would not be included in the PDR supplements. Based on these assumptions, the estimated cost of publishing the extended labeling in the PDR would be about $0.75 million for year 1. These costs would continue to increase over time as all drug approvals after the effective date of the rule

would have longer PDR listings. The estimated annual and total cost of printing longer PDR listings are shown in table 7.

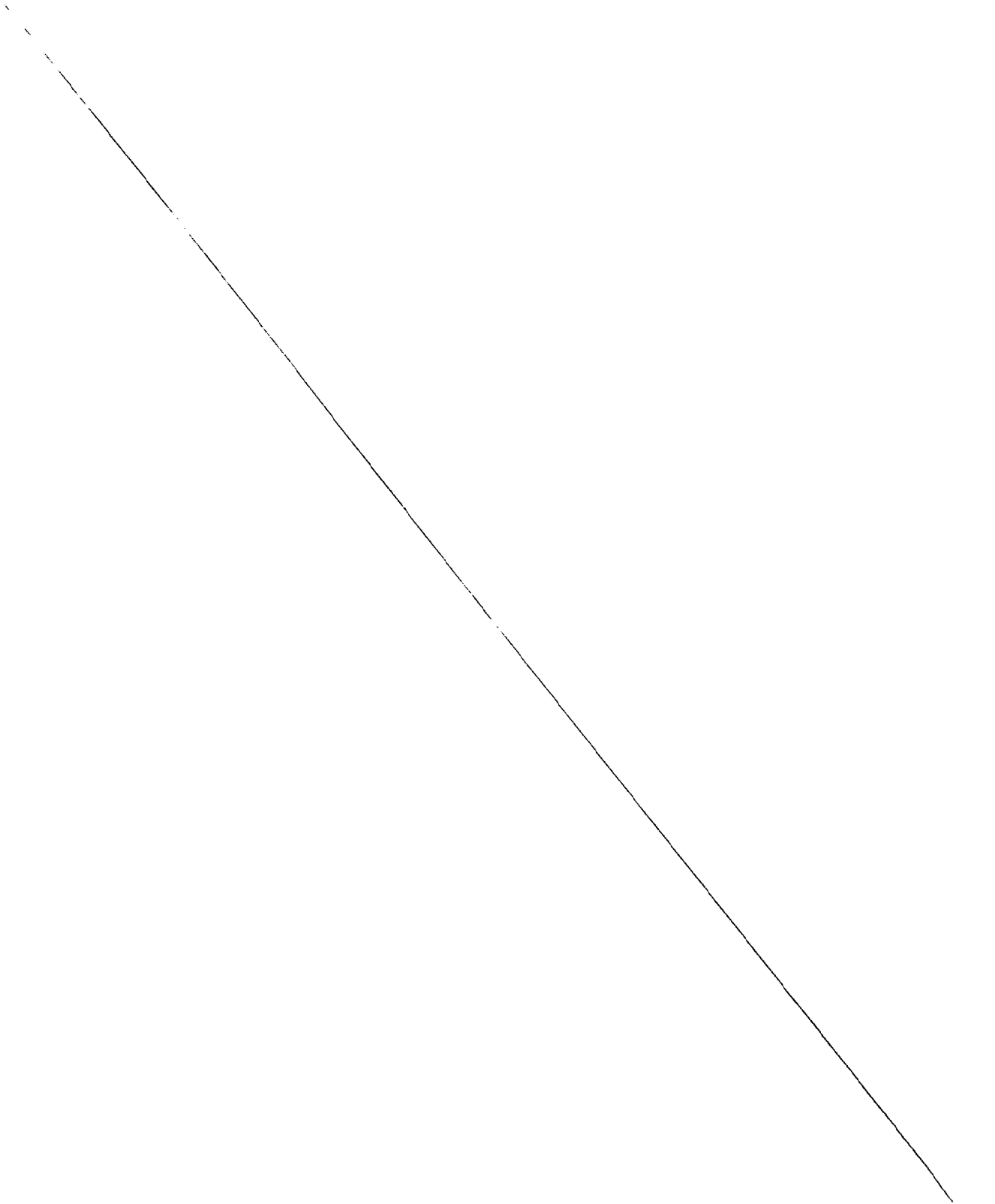


Table 7.-- Cost for Longer Listings in the PDR

Year	PDR Printing Costs ($ million)			
	PDR Bound	Supplement	Total	Present Value
1	$0.47	$0.31	$0.78	$0.73
2	$1.13	$0.47	$1.60	$1.40
3	$1.95	$0.41	$2.36	$1.93
4	$2.68	$0.37	$3.05	$2.32
5	$3.34	$0.35	$3.69	$2.63
6	$3.99	$0.34	$4.33	$2.89
7	$4.62	$0.34	$4.96	$3.09
8	$5.01	$0.34	$5.35	$3.11
9	$5.39	$0.34	$5.73	$3.12
10	$5.78	$0.33	$6.11	$3.11
Total	$34.36	$3.60	$37.96	$24.33

2. Labeling Changes for All Approved Prescription Drug Products

The agency is also proposing several new retrictions for the labeling of all prescription drug products. These changes can be made, without prior FDA approval, upon submission of a "changes being effected" supplement. Labeling for all prescription drug products must comply with the proposed content requirements within 1 year after the effective date of the final rule.

a. Affected products. The proposed rule will no longer allow certain information that is sometimes now included in professional labeling (e.g., discussion of studies not supporting approved indications, suggestion of uses or indications not included in the "Indications and Uses" section, or discussion of in vitro and animal studies on drug action or efficacy that have

not been shown to be pertinent to clinical use by adequate and well-controlled studies). FDA does not know how much product labeling would be affected, but because labeling of most antibiotics currently contains data from in vitro studies, the agency estimates that the proposed rule could affect 90 percent of all antibiotics. Of the approximately 5,300 marketed products in the United States, there are an estimated 789 antibiotics products.[22] Moreover, up to 25 percent of all other marketed products could have labeling containing information that would be prohibited. In the first year, therefore, as many as 1,838 products might have to delete some material from their professional labeling.

In addition, any existing prescription drug product with approved printed patient information or Medication Guide must reprint this information following the last section of the professional labeling. The agency estimates that about 50 approved products, or approximately 1 percent of the existing products, could be affected by this requirement.

b. Professional labeling design costs. Industry consultants estimate that, on average, prescription drug manufacturers would incur about $2,000 per product in design and

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[22]Derived from the 1998 Approved Drug Products With Therapeutic Equivalence Evalutaion (Orange Book), CDER, FDA. Products with NDA numbers in the 50,000 or 60,000 series (i.e., antibiotics), with a distinct dosage form or manufacturer were counted. This number, however, probably overestimates the number of antibiotic products with distinct labeling.

implementation costs for a major revision in the content of professional labeling. Industry consultants with expertise in pharmaceutical labeling estimate that professional labeling inventories represent approximately 3 months worth of production. If given an adequate lead time, companies should be able to minimize inventory losses. This proposed rule would require changes within 1 year of the effective date. Assuming that not all affected firms would have sufficient time to deplete their inventories, consultants estimate the per product professional labeling inventory losses are $570 for a 12 month lead time. Thus, including excess inventory losses, the cost to change professional labeling is estimated at $2,600 per product. In the first year, therefore, firms may incur one-time costs of $4.7 million and $0.1 million, respectively, to remove prohibited material from labeling and to add printed patient information to labeling for all affected products (table 8).

c. Incremental printing costs for professional labeling. FDA estimates that an average of 310,000 package inserts may be printed annually for each prescription drug product marketed in the United States.[23] The removal of prohibited information from professional labeling may reduce the size of current package

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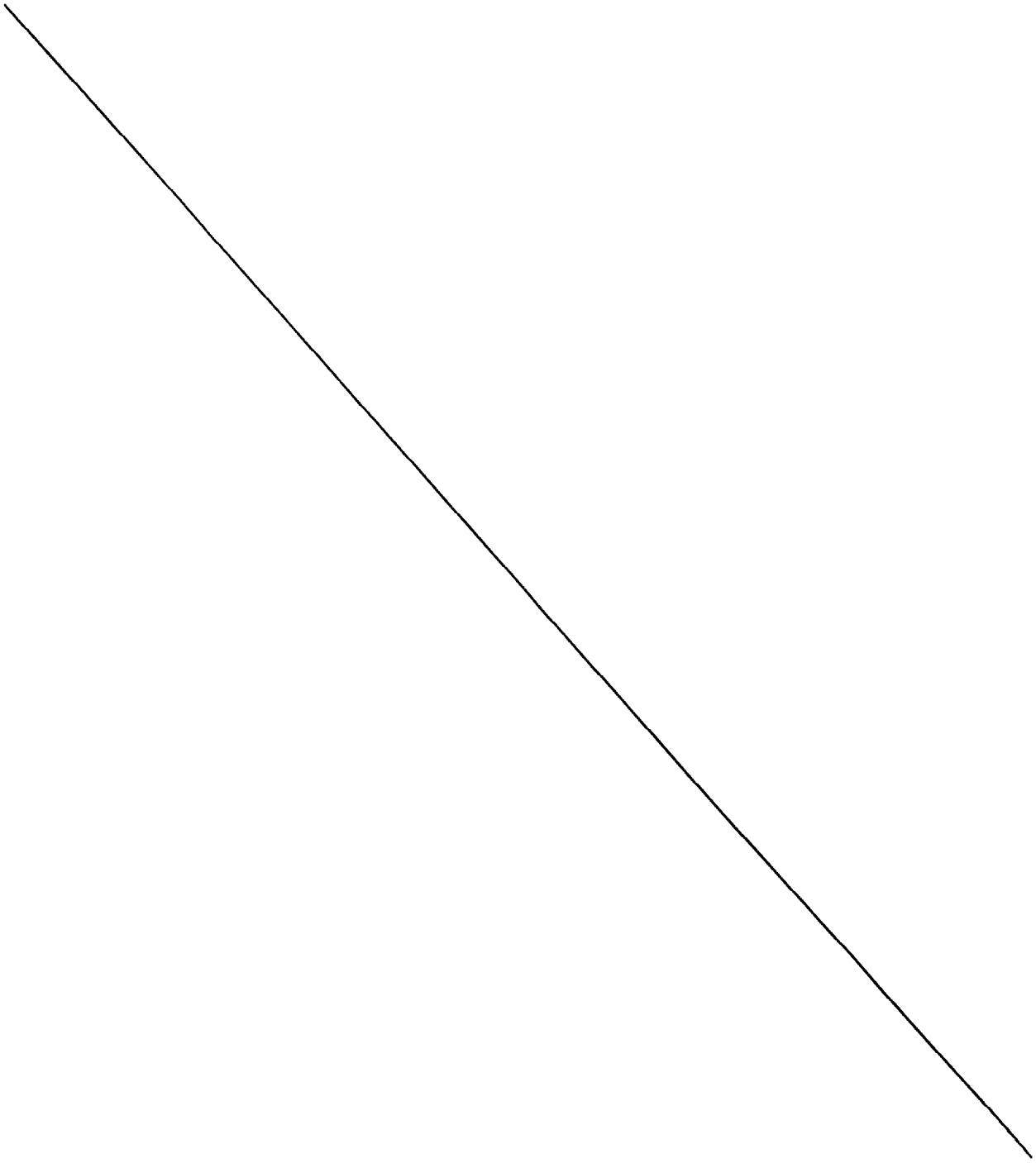
[23]310,000 inserts per product = 1.65 billion inserts printed annually/5,300 products.

inserts by about 3 percent or 3 square inches. With such a small change in the length of professional labeling, it is unlikely that the package insert would actually change size. Therefore,



the agency assumed no cost savings for shorter professional labeling.

In contrast, printed patient information would add an estimated 2 pages or about 75 square inches to the length of professional labeling. For each of the affected products, manufacturers would incur additional incremental printing costs of about $2,000 for longer labeling.[24] For all 50 affected products, annual incremental printing costs would increase by $0.1 million (table 8).

Table 8.--Costs to Revise Professional Labeling of Existing Prescription Product

Changes to Labeling	Number of Affected Products	One-Time Labeling Revision Costs ($million)	Annual Incremental Printing Costs ($million)	Annual PDR Costs ($million)
Removal of prohibited material	1,838	$4.70	$0.00	$0.00
Addition of approved printed patient information or Medication Guide	50	$0.13	$0.10	$0.60
Total	1,888	$4.83	$0.10	$0.60

d. PDR costs. The agency assumes that 75 percent of prescription drug products have labeling already printed in the PDR. In accord with the rationale described above, the annual printing costs for the PDR are estimated to be unchanged for

[24]$2,000 per product = 75 square inches/insert x 0.000086 square inches x 310,000 inserts per product.

products that remove information and to increase for products that add patient information. The per product annual cost to print two additional pages in the PDR is about $16,000.[25] For all affected products, the annual PDR costs would increase by $0.6 million (table 8).

3. Changes to Drug Product Labels

The proposed rule also specifies minor changes to prescription drug product labels to remove excess information from the label to help reduce medication errors. To reduce the burden on industry, changes to labels are not required until the first time labeling is revised after the effective date of the final rule. Therefore, no additional compliance costs are estimated for these changes.

Table 9 displays the estimated compliance costs for the three major cost categories over a 10-year period.

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[25]$16,000 per product = $8,000/ page x 2 pages.

Table 9.--Compliance Cost Over 10-Year Period

Year	Cost Category ($ million)			Total Costs ($ million)
	Labeling Design and FDA Approval	Producing Professional Labeling (including equipment costs)	Printing PDR	
1	$5.55	$2.71	$1.38	$9.64
2	$1.04	$4.77	$2.20	$8.01
3	$1.45	$7.35	$2.96	$11.76
4	$1.31	$8.59	$3.65	$13.54
5	$1.21	$9.25	$4.29	$14.75
6	$1.18	$9.60	$4.93	$15.72
7	$1.16	$10.08	$5.56	$16.79
8	$0.61	$9.78	$5.95	$16.34
9	$0.60	$9.69	$6.33	$16.61
10	$0.59	$9.61	$6.71	$16.91
Total current value	$14.68	$81.43	$43.96	$140.07
Total present value	$11.62	$54.37	$28.54	$94.52

D. Impacts on Small Entities

1. The Need for and the Objectives of the Rule

As discussed in detail in section II of this document, various developments in recent years have contributed to an increase in the length and complexity of prescription drug product labeling, and made it more difficult for health care practitioners to find specific information and discern the most critical information in labeling. The objective of the proposed requirements is to enhance the safe and effective use of

prescription drug products by making it easier for health care practitioners to access, read, and use information in prescription drug product labeling.

As previously stated, FDA's legal authority to amend its regulations governing the content and format of labeling for human prescription drug and biologic products and to amend its regulations governing the requirements for prescription drug product labels derives from sections 201, 301, 501, 502, 503, 505, and 701 of the act (21 U.S.C. 321, 331, 351, 352, 353, 355, and 371) and section 351 of the PHS Act (42 U.S.C. 262).

2. Description and Estimate of the Number of Small Entities Affected

This proposed rule would affect all small entities required to design their prescription drug labeling to comply with this rule. The Small Business Administration (SBA) considers firms in Standardized Industrial Classification Code 2834, Pharmaceutical Preparations, with fewer than 750 employees to be small entities. Although U.S. Census size categories do not correspond to SBA size categories, of the approximately 600 firms identified, over 90 percent have fewer than 500 employees.[26] Thus, most of the firms in the pharmaceutical industry are considered small entities for Regulatory Flexibility Act purposes. In contrast, an agency review of NDA's received in FY 97, 98, and 99 found

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[26]U.S. Department of Commerce, Bureau of the Census, 1992 Census of Manufacturers, Industry Series, Drugs, MC92-1-28C.

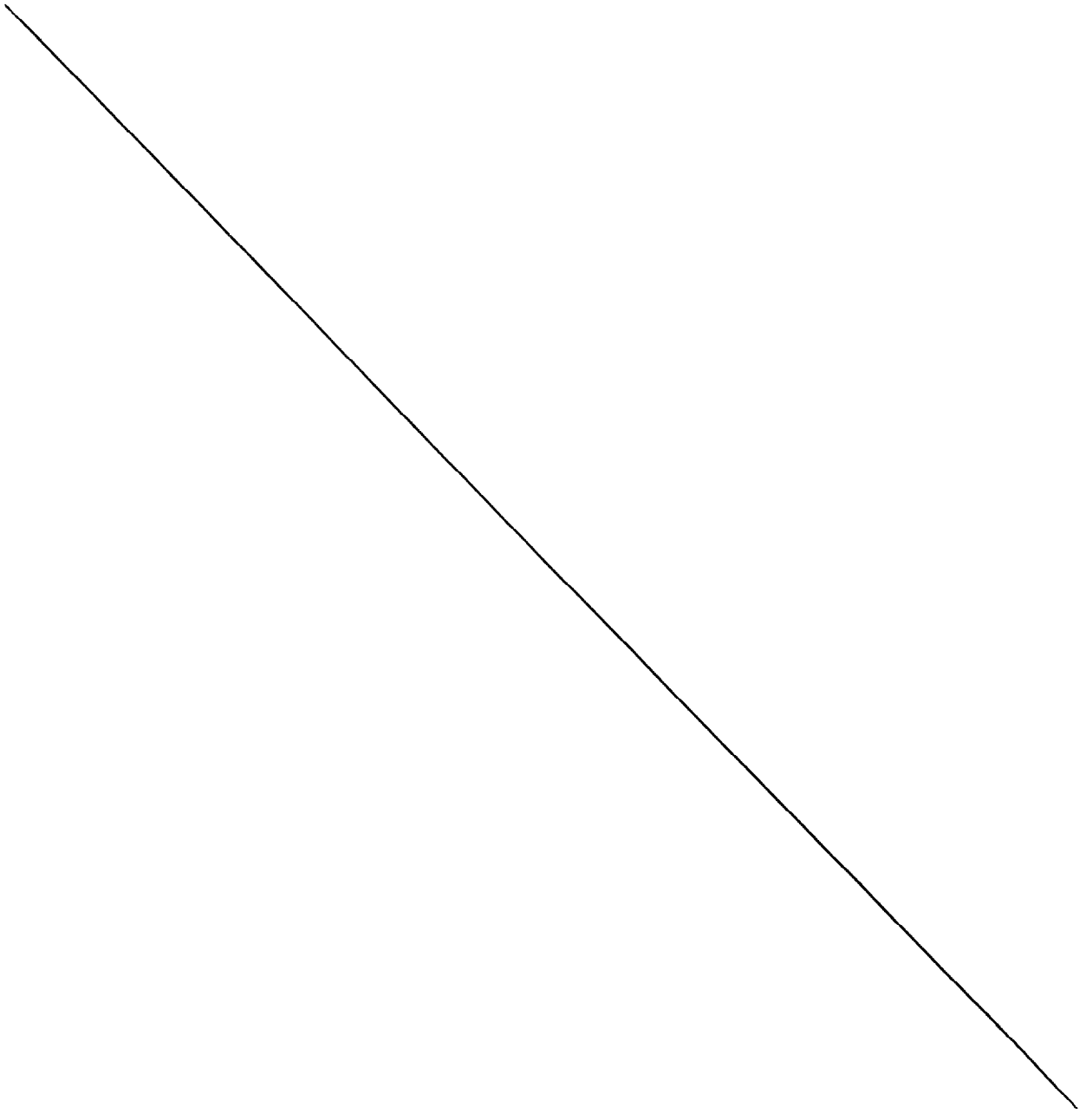
that about 19 small entities submit NDA's each year. In addition, an equal number of small firms that submit BLA's, ES's and/or reformatted professional labeling for approval would also be affected, for a total of about 38.

Census of Manufactures data on revenues per firm apply to all establishments classified in 2834, Pharmaceutical Preparations. As noted above, only a subset of this industry is affected by this rule. The agency does not know the average revenues for the affected sectors.

3. Description of the Compliance Requirements

The compliance requirements for small entities under this proposed rule are the same as those described above for other affected entities. Compliance primarily involves: (1) Designing labeling that conforms to the format requirements as illustrated in the FDA-designed prototype; and (2) once the labeling is approved by FDA, ensuring that all future printed labeling (including labeling used for promotional purposes) is in the new format. Because sponsors already submit labeling with NDA's and supplements to FDA, no additional skills will be required to comply with the proposed rule.

The group of small entities likely to bear the highest total costs under this proposed rule are those firms that have: (1) Existing products with labeling that must be revised in the first year; or (2) more than one affected high-volume product per year, such as a small firm with two or three recently approved, high-volume products that must undergo labeling reformatting



simultaneously in the same year. However, the high-cost small entities are also the small firms with the highest sales of affected product; thus, their incremental cost per unit sold is likely to be relatively low. In contrast, small firms with a single, low-volume product would have lower total costs of compliance, but the incremental cost per unit sold would be higher.

To illustrate the impact on small entities with different production volumes, the following examples estimate the professional labeling costs for a small firm with a single carton-enclosed product (marketed under an NDA) that must: (1) Have its labeling reformatted in year 3 of the rule, and (2) add patient information in year 1. Table 10 outlines the projected per-unit and total costs to the firm under three different levels of production: 1,000, 10,000, and 100,000 units produced per year.

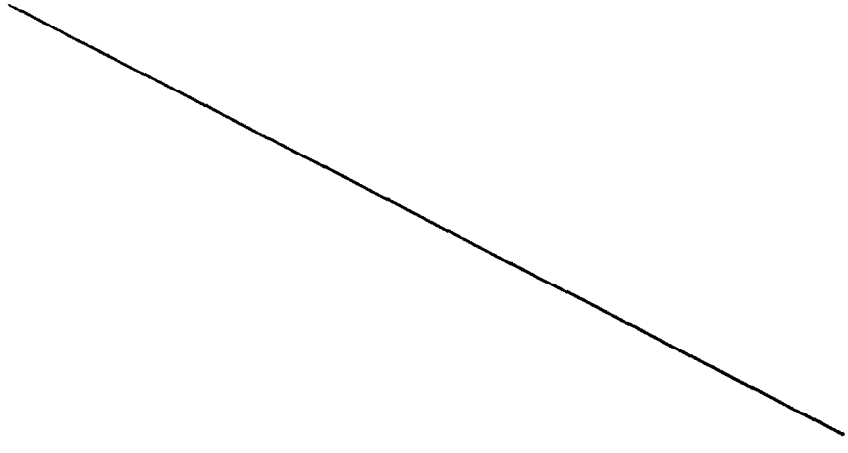


Table 10.--Estimated Costs for Hypothetical Small Firm With a Single Product, Under Three Alternative Levels of Production

Cost Category	Number of Units Produced and Sold Each Year		
	100,000	10,000	1,000
Example 1--Change labeling approved less than 1 year before effective date:			
Professional labeling redesign/ application	$7,500	$7,500	$7,500
Printing package inserts[1]	$876	$88	$9
Printing professional labeling used for promotional purposes[2]	$1,611	$161	$16
Total	$9,987	$7,749	$7,525
Additional cost per unit sold	$0.10	$0.77	$7.53
Example 2--Add patient information to labeling of an existing product:			
Professional labeling redesign	$2,600	$2,600	$2,600
Printing package inserts[3]	$710	$71	$7
Printing longer PDR[4]	$16,000	$16,000	$16,000
Total	$19,310	$18,671	$18,607
Additional cost per unit sold	$0.87	$1.87	$18.61

[1]Number of package inserts printed is calculated as units produced/year plus 10 percent wastage factor, at an incremental printing cost of $.00796 per label.

[2]Incremental costs associated with printing labeling used for promotional purposes are assumed to be 184% of the costs of printing package inserts, based on the ratio of the average number of pieces printed for mailings to the average number printed as package inserts.

[3]Number of package inserts printed is calculated as units produced/year plus 10 percent wastage factor, at an incremental printing cost of $.00645 per package insert.

[4]Assume that professional labeling is already being printed in the PDR.

In addition to the costs identified in table 10, a very small number of small firms might incur equipment costs to include longer prescription drug labeling in carton-enclosed products. It is likely, however, that this one-time capital cost (estimated at $200,000) will affect a total of no more than two or three small firms in the 10 years following implementation of the rule. Based on this analysis, FDA finds that the impact of this proposed rule would not be significant for most small entities in this industry, but it is possible that more than a few small firms may incur significant costs. The agency solicits public comment on the potential impact of the proposed rule on small entities.

4. Alternatives Considered

a. Formatting alternatives. FDA has considered numerous alternative formats, including a longer highlights section. The highlights section was limited to about one-half page to respond

to health professionals' concerns about length as well as to reduce the incremental printing costs to sponsors.

The agency also considered increasing the minimum required font size from 8 point to 10 point. The larger font size would increase labeling by approximately 196 square inches, whereas labeling printed in 8-point font size is estimated to increase by only 93 square inches. Furthermore, the incremental costs for labeling printed in 10 point font size would be approximately $16,850 per million inserts, more than double the incremental costs of labeling printed in 8-point font size. Over 10 years, the total present value of producing longer labeling would increase by $111.5 million with the larger font size, compared to $52.7 million for the 8-point font size. Although the agency has tentatively rejected the minimum 10-point font size requirement because of the additional burden on industry, FDA solicits comment on minimum font size requirements.

b. Alternative categories of affected products. Three alternative categories of products to be covered by the rulemaking were considered: (1) All drugs, (2) a proposed set of innovator and generic drugs on a "top 200 most prescribed" list, and (3) the "top 100" or "top 200" drugs with the most adverse drug reactions. The agency has tentatively rejected these three alternatives because it was uncertain whether the benefits would exceed the costs, especially in the case of older drugs and generic drugs for which physicians infrequently consult labeling.

In addition, the "top 200" lists were excluded because the agency believed that the most important subset of these products would be covered by the currently proposed rule. However, FDA solicits comment on these alternative criteria for selecting drugs to be affected by the rulemaking.

c. Alternative implementation schedule. FDA considered a shorter implementation schedule, requiring that the labeling for all applications and efficacy supplements approved 5 years prior to the implementation date be revised 3 years after the effective date. The more gradual implementation schedule has been proposed primarily to reduce the impact of the rule on small entities as well as the immediate impact of the rulemaking on the industry as a whole.

XI. Request for Comments

Interested persons may submit to the Dockets Management Branch (address above) written comments regarding this proposal by [insert date 90 days after date of publication in the FEDERAL REGISTER]. Two copies of any comments are to be submitted, except that individuals may submit one copy. Comments are to be identified with the docket number found in brackets in the heading of this document. Received comments may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday.

XII. References

The following references have been placed on display in the Dockets Management Branch (address above) and may be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday.

1. LittleJohn, J. K., "Package Insert: View of a Rural Town Practitioner," Drug Information Journal, vol. 21, pp. 63-65, 1987.

2. National BioSystems, Inc., "Focus Group Report: Physician's Perceptions of Prescription Drug Labeling Information," Contract #223-91-3501, February 1992.

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13. Pharmacopeial Forum, vol. 20, No. 4, pp. 7885-7887, July and August 1994.

14. Randolph, L., Physician Characteristics and Distribution in the United States, 1997/1998 ed., Chicago, IL, American Medical Association, 1998.

15. Classen, D. C. et al., "Adverse Drug Events in Hospitalized Patients: Excess Length of Stay, Extra Costs, and Attributable Mortality," Journal of the American Medical Association, vol. 277, pp. 301-306, 1997.

16. Bates, D. W. et al., "Incidence of Adverse Drug Events and Potential Adverse Drug Events," Journal of the American Medical Association, vol. 274, pp. 29-34, 1995.

17. Bates, D. W. et al., "The Costs of Adverse Drug Events in Hospitalized Patients," Journal of the American Medical Association, vol. 277, pp. 307-311, 1997.

List of Subjects in 21 CFR Part 201

Drugs, Labeling, Reporting and recordkeeping requirements.

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, it is proposed that 21 CFR part 201 be amended as follows:

PART 201--LABELING

1. The authority citation for 21 CFR part 201 continues to read as follows:

Authority: 21 U.S.C. 321, 331, 351, 352, 353, 355, 358, 360, 360b, 360gg-360ss, 371, 374, 379e; 42 U.S.C. 216, 241, 262, 264.

§ 201.55 [Amended]

2. Section 201.55 Statement of dosage is amended by revising the third sentence to read as follows: "When this occurs, a statement of the recommended or usual dosage is not required on the label or carton."

3. Section 201.56 is revised to read as follows:

§ 201.56 Requirements on content and format of labeling for human prescription drugs and biologics.

(a) General requirements. Prescription drug labeling described in § 201.100(d) must meet the following general requirements:

(1) The labeling must contain a summary of the essential scientific information needed for the safe and effective use of the drug.

(2) The labeling must be informative and accurate and neither promotional in tone nor false or misleading in any particular.

(3) The labeling must be based whenever possible on data derived from human experience. No implied claims or suggestions of drug use may be made if there is inadequate evidence of safety or a lack of substantial evidence of effectiveness. Conclusions based on animal data but necessary for safe and effective use of the drug in humans shall be identified as such and included with human data in the appropriate section of the labeling.

(b) Categories of prescription drugs subject to the labeling content and format requirements in §§ 201.56(d) and 201.57. (1) The following categories of prescription drug products are subject to the labeling requirements in paragraph (d) of this section and § 201.57 in accordance with the implementation schedule in paragraph (c) of this section:

(i) Prescription drug products for which a new drug application (NDA), biological license application (BLA), or efficacy supplement has been approved by the Food and Drug Administration (FDA) anytime from 0 up to and including 5 years before [effective date of final rule];

(ii) Prescription drug products for which an NDA, BLA, or efficacy supplement is pending on [effective date of final rule]; or

(iii) Prescription drug products for which an NDA, BLA, or efficacy supplement is submitted anytime on or after [insert effective date of final rule].

(2) Prescription drug products not described in paragraph (b)(1) of this section are subject to the labeling requirements in paragraph (e) of this section and § 201.80.

(c) Schedule for implementing the labeling content and format requirements in §§ 201.56(d) and 201.57. For products described in paragraph (b)(1) of this section, labeling conforming to the requirements in paragraph (d) of this section and § 201.57 must be submitted according to the following schedule:

(1) For products for which an NDA, BLA, or efficacy supplement is submitted for approval on or after [effective date of the final rule], proposed conforming labeling must be submitted as part of the application.

(2) For products for which an NDA, BLA, or efficacy supplement is pending at [effective date of final rule], or that has been approved any time from [effective date of final rule] up to and including 1 year before [effective date of final rule], a supplement with proposed conforming labeling must be submitted no later than 3 years after [effective date of the final rule].

(3) For products for which an NDA, BLA, or efficacy supplement has been approved from 1 year up to and including 2 years before [effective date of final rule], a supplement with proposed conforming labeling must be submitted no later than 4 years after [effective date of the final rule].

(4) For products for which an NDA, BLA, or efficacy supplement has been approved from 2 years up to and including 3 years before [effective date of final rule], a supplement with proposed conforming labeling must be submitted no later than 5 years after [effective date of the final rule].

(5) For products for which an NDA, BLA, or efficacy supplement has been approved from 3 years up to and including 4 years before [effective date of final rule], a supplement with proposed conforming labeling must be submitted no later than 6 years after [effective date of the final rule].

(6) For products for which an NDA, BLA, or efficacy supplement has been approved from 4 years up to and including 5 years before [effective date of the final rule], a supplement

with proposed conforming labeling must be submitted no later than 7 years after [effective date of the final rule].

(d) Labeling requirements for newly and more recently approved prescription drug products. This paragraph applies only to prescription drug products described in paragraph (b)(1) of this section and must be implemented according to the schedule specified in paragraph (c) of this section.

(1) Prescription drug labeling described in § 201.100(d) must contain the specific information required under § 201.57(a), (b), and (c) under the following section headings and subheadings and in the following order:

Highlights of Prescribing Information

Product Names, Other Required and Optional Information

Boxed Warning

Recent Labeling Changes

Indications and Usage

Dosage and Administration

How Supplied

Contraindications

Warnings/Precautions

Drug Interactions

Use in Specific Populations

Comprehensive Prescribing Information: Index

Comprehensive Prescribing Information

!Boxed Warning

1 Indications and Usage

2 Dosage and Administration

3 How Supplied/Storage and Handling

4 Contraindications

5 Warnings/Precautions

6 Drug Interactions

7 Use in Specific Populations

- 7.1 Pregnancy
- 7.2 Labor and delivery
- 7.3 Lactating women
- 7.4 Pediatric use
- 7.5 Geriatric use

8 Adverse Reactions

9 Drug Abuse and Dependence

10 Overdosage

11 Description

12 Clinical Pharmacology

- 12.1 Mechanism of action
- 12.2 Pharmacodynamics
- 12.3 Pharmacokinetics
- 12.4 Other clinical pharmacology information

13 Nonclinical Toxicology

- 13.1 Carcinogenesis, mutagenesis, impairment of fertility
- 13.2 Animal toxicology and/or pharmacology

14 Clinical Studies

P Patient Counseling Information

(2) The labeling may contain an additional section entitled "R References" if appropriate and if in compliance with § 201.57(c)(16).

(3) Sections or subsections of the labeling required under § 201.57(a), (b), or (c) may be omitted if clearly inapplicable.

(4) The labeling required under § 201.57(c) may contain a "Product Title" section preceding any boxed warning as required in § 201.57(c)(1) or, in the absence of such warning, preceding the "Indications and Usage" section, and containing only the information required by §§ 201.57(c)(12)(i)(A) through (c)(12)(i)(D) and 201.100(e). The information required by § 201.57(c)(12)(i)(A) through (c)(12)(i)(D) must appear in the "Description" section of the labeling, whether or not it also appears in a "Product Title" section.

(5) The labeling required under § 201.57(c) may include additional nonstandardized subheadings under the standardized subheadings listed in paragraphs (d)(1) and (d)(2) of this section to emphasize specific topics within the text of the required sections where the use of additional subheadings will enhance labeling organization, presentation, or ease of use (e.g., subheadings may be used to set off individual warnings or precautions, or for each drug interaction). If additional subheadings are used, they must be assigned a decimal index

number that corresponds to their placement in labeling and is consistent with the standardized index numbers and identifiers listed in paragraphs (d)(1) and (d)(2) of this section (e.g., subheadings added to the "Warnings/Precautions" subsection could be numbered 5.1, 5.2, and so on; subheadings in the "Patient Counseling Information" subsection could be numbered P.1, P.2, and so on).

(e) Labeling requirements for older prescription drug products. This paragraph applies only to approved prescription drug products not described in paragraph (b)(1) of this section.

(1) Prescription drug labeling described in § 201.100(d) must contain the specific information required under § 201.80 under the following section headings and in the following order:

Description

Clinical Pharmacology

Indications and Usage

Contraindications

Warnings

Precautions

Adverse Reactions

Drug Abuse and Dependence

Overdosage

Dosage and Administration

How Supplied

(2) The labeling may contain the following additional section headings if appropriate and if in compliance with § 201.80(l) and (m):

Animal Pharmacology and/or Animal Toxicology

Clinical Studies

References

(3) The labeling may omit any section or subsection of the labeling format if clearly inapplicable.

(4) The labeling may contain a "Product Title" section preceding the "Description" section and containing only the information required by § 201.80(a)(1)(i), (a)(1)(ii), (a)(1)(iii), and (a)(1)(iv) and § 201.100(e). The information required by § 201.80(a)(1)(i) through (a)(1)(iv) shall appear in the "Description" section of the labeling, whether or not it also appears in a "Product Title."

(5) The labeling must contain the date of the most recent revision of the labeling, identified as such, placed prominently after the last section of the labeling.

4. Section 201.57 is redesignated as § 201.80 and new § 201.57 is added to read as follows:

§ 201.57 Specific requirements on content and format of labeling for human prescription drugs and biologic products described in § 201.56(b)(1).

The requirements in this section apply only to prescription drug products described in § 201.56(b)(1) and must be implemented

according to the schedule specified in § 201.5(c), except for the requirements in paragraphs (c)(2)(ii), (c)(2)(iii), (c)(3), (c)(13)(ii), (c)(15)(i), and (c)(17) of this section, which must be implemented no later than 1 year after [effective date of the final rule].

(a) Highlights of prescribing information. This section must appear in all prescription drug labeling. Statements made in promotional labeling and advertisements must be consistent with all information included in labeling under paragraph (c) of this section in order to comply with § 202.1(e) and § 201.100(d)(1) of this chapter. The section must include the following information under the identified subheading, if any, in the following order:

(1) Drug names, dosage form, route of administration and controlled substance symbol. The proprietary name and the established name of the drug, if any, as defined in section 502(e)(3) of the Federal Food, Drug, and Cosmetic Act (the act) or, for biological products, the proper name (as defined in § 600.3 of this chapter) including any appropriate descriptors. This information must be followed by the drug's dosage form and route of administration. For controlled substances, the controlled substance symbol designating the schedule in which the controlled substance is listed.

(2) Inverted black triangle symbol. The "▼" symbol if the drug product has been approved for less than 3 years in the

United States and contains a new molecular entity or new biological product, a new combination of active ingredients, is indicated for a new population, is administered by a new route, or uses a novel drug delivery system. This symbol must be placed on the same line as the proprietary name of the product, or the established or proper name if there is no proprietary name.

(3) Prescription drug symbol. The ℞ symbol to indicate that the drug is a prescription drug. This symbol must be placed on the same line as the proprietary name of the product, or the established or proper name if there is no proprietary name, immediately following any "▼" symbol.

(4) Boxed warnings or contraindications. The full text of any boxed warning or contraindication required by paragraph (c)(1) of this section, provided that the text does not exceed a length of 20 lines. Where the text exceeds 20 lines, a statement summarizing the contents of the boxed warning(s) or contraindication(s) must be included, also not to exceed a length of 20 lines. The boxed warning or summary statement of the boxed warning must be preceded by a heading, in upper-case letters, containing the word "WARNING(S)" and other words that are appropriate to identify the subject of the warning. Both the text of the boxed warning or summary statement of the boxed warning and heading must be contained within a box and bolded. For summary statements of a boxed warning, the following

statement shall be placed immediately following the heading of the boxed warning: "See ! for full boxed warning."

(5) Recent labeling changes. A listing of the section(s) of the comprehensive prescribing information in paragraph (c) of this section that contain(s) substantive labeling changes that have been approved by FDA or authorized under § 314.70(c)(2) or (d)(2) of this chapter, or § 601.12(f)(1) through (f)(3) of this chapter. The heading(s) and, if appropriate, the subheading(s) of the labeling section(s) affected by the change must be listed together with each section's index number or identifier. This section must be retained in the labeling for at least 1 year after the date of the labeling change, and may be retained until such time that the labeling is reprinted for the first time following the change.

(6) Indications and usage. A concise statement of each of the product's indications as required under paragraph (c)(2) of this section, with any appropriate subheadings. Major limitations of use (e.g., particular subsets of the population, second line therapy status, or antimicrobials limited to certain microorganisms) must be briefly noted.

(7) Dosage and administration. The most important aspects of the comprehensive prescribing information required under paragraph (c)(3) of this section, with any appropriate subheadings. This would include the most common dosage regimen(s) and critical differences among population subsets,

monitoring requirements, and other therapeutically important clinical pharmacologic information. The use of tables is encouraged, where appropriate (e.g., when there are different dosage regimens for different indications).

(8) How supplied. A concise summary of information concerning the product's dosage form(s) that is required under paragraph (c)(4) of this section. This would ordinarily include the metric strength or strengths of the dosage form and whether the product is scored. If appropriate, the information in this section of the labeling should include subheadings to specify different dosage forms (e.g., tablets, capsules, injectables, suspension).

(9) Contraindications. A concise summary of the comprehensive prescribing information required under paragraph (c)(5) of this section, with any appropriate subheadings.

(10) Warnings/precautions. A concise summary of the most clinically significant aspects of the comprehensive prescribing information required under paragraph (c)(6) of this section, with any appropriate subheadings. Clinically significant warnings and precautions include those that affect prescribing because of their severity and consequent influence on the decision to use the drug, because it is critical to safe use of the drug to monitor patients for them, or because measures can be taken to prevent or mitigate harm. This section of the the labeling must also include the subheading "Most Common Adverse Reactions

(≥ n/100)." Under this subheading, the most frequently occurring adverse reactions (i.e., noxious and unintended responses for which there is a reasonable causal association with the use of the drug), as described in paragraph (c)(9) of this section, must be listed along with the incidence rate used to determine inclusion. Typically, the incidence rate for inclusion would be expected to be ≥ 1/100. When appropriate, adverse reactions important for other reasons (e.g., because they lead to discontinuation or dosage adjustment) may be included.

(11) ADR reporting contacts. For drug products other than vaccines, the verbatim statement "To report SUSPECTED SERIOUS ADR's, call (insert name of manufacturer) at (insert manufacturer's phone number) or FDA's MedWatch at (insert current FDA MedWatch number)." For vaccines, the verbatim statement "To report SUSPECTED SERIOUS ADR's, call (insert name of manufacturer) at (insert manufacturer's phone number) or VAERS at (insert the current VAERS number)."

(12) Drug interactions. A concise summary of other prescription and over-the-counter drugs or foods that interact in clinically significant ways with the product, from the comprehensive prescribing information required under paragraph (c)(7) of this section, with any appropriate subheadings.

(13) Use in specific populations. A concise summary of any clinically important differences in response or use of the drug in specific populations, from the comprehensive prescribing

information required under paragraph (c)(8) of this section, with any appropriate subheadings.

(14) Patient counseling information statement. When applicable, the verbatim statement "See P for Patient Counseling Information." If the product has approved patient labeling or a Medication Guide, the verbatim statement "See P for Patient Counseling Information, followed by (insert name of drug)'s (insert either approved patient labeling or Medication Guide)."

(15) Highlights limitation statement. The verbatim statement "These highlights do not include all the information needed to prescribe (insert name of drug product) safely and effectively. See (insert name of drug product)'s comprehensive prescribing information provided below."

(16) Revision date. The date of the most recent revision of the labeling, identified as such, placed at the end of the highlights section.

(17) Index number placement. Any subheadings required by paragraphs (a)(4) through (a)(10), (a)(12), and (a)(13) of this section, as well as additional subheadings included in the highlights section of the labeling under § 201.56(d)(5), must be followed by their index number in parentheses.

(b) Comprehensive prescribing information: Index. This section must appear in all prescription drug labeling immediately following the information required under paragraph (a) of this section and must contain a list of each subheading required under

§ 201.56(d)(1), if not omitted under § 201.56(d)(3), preceded by the index number or identifier required under § 201.56(d)(1) or (d)(2). The section must also contain additional subheading(s) included in the comprehensive prescribing information section of labeling under § 201.56(d)(5), preceded by the index number or identifier assigned under that section of the labeling.

(c) Comprehensive prescribing information. This section must appear in prescription drug labeling immediately following the information required under paragraph (b) of this section. The section of the labeling must contain the information in the order required under paragraphs (c)(1) through (c)(17) of this section, together with the subheadings and index numbers or identifiers required under § 201.56(d)(1), unless omitted under § 201.56(d)(3). If additional subheadings are used within a labeling subsection in accordance with § 201.56(d)(5), they must be preceded by the index number assigned under that section.

(1) Boxed warnings and contraindications. Special problems, particularly those that may lead to death or serious injury, may be required by FDA to be placed in a prominently displayed box. The boxed warning(s) or contraindication(s) ordinarily must be based on clinical data, but serious animal toxicity may also be the basis of boxed information in the absence of clinical data. If a box containing warning(s) or contraindication(s) is required, it must be located preceding the "Indications and Usage" section of the labeling. The box must be

preceded by an exclamation point (!) and must contain, in uppercase letters, a heading inside the box that includes the word "WARNING(S)" and is appropriate to communicate the general focus of the boxed information. If the information related to the boxed risk is extensive, the detailed information must be included under a bolded subheading in the appropriate section of the labeling (either "Contraindications" or "Warnings/Precautions"). The brief explanation of the risk(s) in the box must be followed by a reference (i.e., the appropriate index number) to this more detailed information.

(2) 1 Indications and usage. (i) This section of the labeling must state that:

(A) The drug is indicated in the treatment, prevention, mitigation, cure, or diagnosis of a recognized disease or condition; and/or

(B) The drug is indicated for the treatment, prevention, mitigation, cure, or diagnosis of an important manifestation of a recognized disease or condition; and/or

.(c) The drug is indicated for the relief of symptoms associated with a recognized disease or syndrome; and/or

(D) The drug, if used for a particular indication only in conjunction with a primary mode of therapy (e.g., diet, surgery, behavior changes, or some other drug), is an adjunct to the mode of therapy.

(ii) For drug products other than biologics, all indications listed in this section of the labeling must be supported by substantial evidence of effectiveness based on adequate and well-controlled studies as defined in § 314.126(b) of this chapter unless the requirement is waived under § 201.58 or § 314.126(c) of this chapter. Indications or uses must not be implied or suggested in other sections of labeling if not included in this section.

(iii) For biologics, all indications listed in this section of the labeling must be supported by substantial evidence of effectiveness. Indications or uses must not be implied or suggested in other sections of labeling if not included in this section of the labeling.

(iv) This section of the labeling must also contain the following additional information:

(A) If evidence is available to support the safety and effectiveness of the drug or biologic only in selected subgroups of the larger population with a disease, syndrome, manifestation, or symptom under consideration (e.g., patients with mild disease or patients in a special age group), or if evidence to support the indication is based on surrogate endpoints (e.g., CD4 cell counts or viral load), this section of the labeling must succinctly describe the available evidence and state the limitations of usefulness of the drug. In such cases, reference should be made to the "Clinical Studies" section of the labeling

for a detailed discussion of the methodology and results of clinical studies relevant to such limitation(s). The labeling must also identify specific tests needed for selection or monitoring of the patients who need the drug (e.g., microbe susceptibility tests). Information on the approximate kind, degree, and duration of improvement to be anticipated must be stated if available and for all drugs except biological products must be based on substantial evidence derived from adequate and well-controlled studies as defined in § 314.126(b) of this chapter unless the requirement is waived under § 201.58 or § 314.126(c) of this chapter. For biological products, such information must be based upon substantial evidence. If the information is relevant to the recommended intervals between doses, the usual duration of treatment, or any modification of dosage, it must be stated in the "Dosage and Administration" section of the labeling and referenced in this section of the labeling.

(B) If safety considerations are such that the drug should be reserved for certain situations (e.g., cases refractory to other drugs), this information must be stated in this section of the labeling.

(C) If there are specific conditions that should be met before the drug is used on a long-term basis (e.g., demonstration of responsiveness to the drug in a short-term trial in a given

patient), the labeling must identify the conditions; or, if the indications for long-term use are different from those for short-term use, the labeling must identify the specific indications for each use.

(D) If there is a common belief that the drug may be effective for a certain use or if there is a common use of the drug for a condition, but the preponderance of evidence related to the use or condition shows that the drug is ineffective or that the therapeutic benefits of the product do not generally outweigh its risks, FDA may require that the labeling state that there is a lack of evidence that the drug is effective or safe for that use or condition.

(E) Any statements comparing the safety or effectiveness, either greater or less, of the drug with other agents for the same indication must, except for biological products, be supported by substantial evidence derived from adequate and well-controlled studies as defined in § 314.126(b) of this chapter unless this requirement is waived under § 201.58 or § 314.126(c) of this chapter. For biological products, such statements must be supported by substantial evidence.

(3) 2 Dosage and administration. This section of the labeling must state the recommended usual dose, the usual dosage range, and, if appropriate, an upper limit beyond which safety and effectiveness have not been established. Dosages must be stated for each indication and subpopulation when appropriate.

Dosing regimens must not be implied or suggested in other sections of labeling if not included in this section of the labeling. When established and clinically important, efficacious and/or toxic drug and/or metabolite concentration ranges and therapeutic concentration windows for drug and/or metabolites must be stated in this section of the labeling. Information on therapeutic drug concentration monitoring (TDM) must also be included in this section of the labeling when TDM is clinically necessary. This section of the labeling must also state the intervals recommended between doses, the optimal method of titrating dosage, the usual duration of treatment, and any modification of dosage needed in special patient populations (e.g., in children, in geriatric age groups, or in patients with renal or hepatic disease). Specific tables or monographs should be used when they would clarify dosage schedules. Radiation dosimetry information must be stated for both the patient receiving a radioactive drug and the person administering it. This section of the labeling must also contain specific direction on dilution, preparation (including the strength of the final dosage solution, when prepared according to instructions, in terms of milligrams of active ingredient per milliliter of reconstituted solution, unless another measure of the strength is more appropriate), and administration of the dosage form, if needed (e.g., the rate of administration of parenteral drug in milligrams per minute; storage conditions for stability of the

drug or reconstituted drug, when important; essential information on drug incompatibilities if the drug is mixed in vitro with other drugs; and the following statement for parenterals: "Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.")

(4) 3 How supplied/storage and handling. This section of the labeling must contain information on the available dosage forms to which the labeling applies and for which the manufacturer or distributor is responsible. The information must ordinarily include:

(i) The strength or potency of the dosage form in metric system (e.g., 10-milligram tablets), and, if the apothecary system is used, a statement of the strength must be placed in parentheses after the metric designation;

(ii) The units in which the dosage form is ordinarily available for prescribing by practitioners (e.g., bottles of 100);

(iii) Appropriate information to facilitate identification of the dosage forms, such as shape, color, coating, scoring, and National Drug Code number; and

(iv) Special handling and storage conditions.

(v) A statement directed to the pharmacist specifying the type of container to be used in dispensing the drug product to maintain its identity, strength, quality, and purity. Where

there are standards and test procedures for determining that the container meets the requirements for specified types of containers as defined in an official compendium, such terms may be used. For example, "Dispense in tight, light-resistant container as defined in the National Formulary." Where standards and test procedures for determining the types of containers to be used in dispensing the drug product are not included in an official compendium, the specific container or types of containers known to be adequate to maintain the identity, strength, quality, and purity of the drug products must be described. For example, "Dispense in containers that (statement of specifications that clearly enable the dispensing pharmacist to select an adequate container)."

(5) 4 Contraindications. This section of the labeling must describe those situations in which the drug should not be used because the risk of use clearly outweighs any possible therapeutic benefit. These situations include administration of the drug to patients known to have a severe hypersensitivity reaction to it; use of the drug in patients who, because of their particular age, sex, concomitant therapy, disease state, or other condition, have a substantial risk of being harmed by it; or continued use of the drug in the face of an unacceptably hazardous adverse reaction. Known hazards and not theoretical possibilities must be listed (e.g., if severe hypersensitivity to the drug has not been demonstrated, it should not be listed as a

contraindication). If no contraindications are known, this section of the labeling must state "None known."

(6) 5 Warnings/precautions. (i) General. Under this section heading, the labeling must describe clinically significant adverse reactions and other potential safety hazards, including those resulting from drug/drug interactions; limitations in use imposed by them; and steps that should be taken if they occur. The labeling must be revised to include a warning as soon as there is reasonable evidence of an association of a clinically significant hazard with a drug; a causal relationship need not have been definitely established. A specific warning relating to a use not provided for under the "Indications and Usage" section of the labeling may be required by FDA if the drug is commonly prescribed for a disease or condition, and there is lack of substantial evidence of effectiveness for that disease or condition, and such usage is associated with clinically significant risk or hazard. The frequency of all clinically significant adverse reactions (including those that do not require a boxed warning) and, if known, the approximate mortality and morbidity rates for patients sustaining the reaction, which are important to safe and effective use of the drug, must be expressed as provided under the "Adverse Reactions" section of the labeling.

(ii) Other special care precautions. This section of the labeling must also contain information regarding any special care

to be exercised by the practitioner for safe and effective use of the drug (e.g., precautions not required under any other specific section or subsection of the labeling).

(iii) Monitoring: Laboratory tests. This subsection of the labeling must identify any laboratory tests that may be helpful in following the patient's response or in identifying possible adverse reactions. If appropriate, information must be provided on such factors as the range of normal and abnormal values expected in the particular situation and the recommended frequency with which tests should be performed before, during, and after therapy.

(iv) Interference with laboratory tests. If the product is known to interfere with laboratory tests, this subsection of the labeling must briefly note this interference and reference where the detailed information is discussed (typically this will be under the "Drug Interactions" section).

(v) ADR reporting contacts. This section of the labeling must include the statement: "To report SUSPECTED SERIOUS ADR's, call (insert name of manufacturer) at (insert manufacturer's phone number) or FDA's MedWatch at (insert current FDA MedWatch number)." For vaccines, this section of the labeling must include the statement: "To report SUSPECTED SERIOUS ADR's, call (insert name of manufacturer) at (insert manufacturer's phone number) or VAERS at (insert the current VAERS number)."

(7) 6 Drug interactions. (i) This section of the labeling must contain specific practical guidance for the practitioner on preventing clinically significant drug/drug interactions with other prescription or over-the-counter drugs, and drug/food interactions (for example, interactions with dietary supplements and such foods as grapefruit juice) that may occur in patients taking the drug. Specific drugs or classes of drugs with which the drug to which the labeling applies may interact in vivo must be identified, and the mechanism(s) of the interaction must be briefly described. Information in this section of the labeling must be limited to that pertaining to clinical use of the drug in patients. Drug interactions supported only by animal or in vitro experiments should not ordinarily be included, but animal or in vitro data may be used if shown to be clinically relevant. Interactions that have particularly serious consequences may be described briefly in the "Contraindications" or "Warnings/Precautions" sections of labeling, as appropriate, with a more complete description under this section of the labeling. Drug incompatibilities, i.e., drug interactions that may occur when drugs are mixed in vitro, as in a solution for intravenous administration, must be discussed under the "Dosage and Administration" section of the labeling rather than under this section of the labeling.

(ii) This section of the labeling must also contain practical guidance on known interference of the drug with laboratory tests.

(8) 7 Use in specific populations. This section of the labeling must contain the following subsections:

(i) 7.1 Pregnancy. This subsection of the labeling may be omitted only if the drug is not absorbed systemically and the drug is not known to have a potential for indirect harm to the fetus. For all other drugs, this subsection of the labeling must contain the following information:

(A) Teratogenic effects. Under this subheading, the labeling must identify one of the following categories that applies to the drug, and the labeling must bear the statement required under the category:

(1) Pregnancy category A. If adequate and well-controlled studies in pregnant women have failed to demonstrate a risk to the fetus in the first trimester of pregnancy (and there is no evidence of a risk in later trimesters), the labeling must state: "Pregnancy Category A. Studies in pregnant women have not shown that (name of drug) increases the risk of fetal abnormalities if administered during the first (second, third, or all) trimester(s) of pregnancy. If this drug is used during pregnancy, the possibility of fetal harm appears remote. Because studies cannot rule out the possibility of harm, however, (name of drug) should be used during pregnancy only if clearly needed."

The labeling must also contain a description of the human studies. If animal reproduction studies are also available and they fail to demonstrate a risk to the fetus, the labeling must also state: "Reproduction studies have been performed in (kinds of animal(s)) at doses up to (x) times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to (name of drug)." The labeling must also contain a description of available data on the effect of the drug on the later growth, development, and functional maturation of the child.

(2) Pregnancy category B. If animal reproduction studies have failed to demonstrate a risk to the fetus and there are no adequate and well-controlled studies in pregnant women, the labeling must state: "Pregnancy Category B. Reproduction studies have been performed in (kind(s) of animal(s)) at doses up to (x) times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to (name of drug). There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed." If animal reproduction studies have shown an adverse effect (other than decrease in fertility), but adequate and well-controlled studies in pregnant women have failed to demonstrate a risk to the fetus during the first trimester of pregnancy (and there is no evidence of a risk

in later trimesters), the labeling must state: "Pregnancy Category B. Reproduction studies in (kind(s) of animal(s)) have shown (describe findings) at (x) times the human dose. Studies in pregnant women, however, have not shown that (name of drug) increases the risk of abnormalities when administered during the first (second, third, or all) trimester(s) of pregnancy. Despite the animal findings, it would appear that the possibility of fetal harm is remote, if the drug is used during pregnancy. Nevertheless, because the studies in humans cannot rule out the possibility of harm, (name of drug) should be used during pregnancy only if clearly needed." The labeling must also contain a description of the human studies and a description of available data on the effect of the drug on the later growth, development, and functional maturation of the child.

(3) Pregnancy category C. If animal reproduction studies have shown an adverse effect on the fetus, if there are no adequate and well-controlled studies in humans, and if the benefits from the use of the drug in pregnant women may be acceptable despite its potential risks, the labeling must state: "Pregnancy Category C. (Name of drug) has been shown to be teratogenic (or to have an embryocidal effect or other adverse effect) in (name(s) of species) when given in doses (x) times the human dose. There are no adequate and well-controlled studies in pregnant women. (Name of drug) should be used during pregnancy only if the potential benefit justifies the potential risk to the

fetus." The labeling must contain a description of the animal studies. If there are no animal reproduction studies and no adequate and well-controlled studies in humans, the labeling must state: "Pregnancy Category C. Animal reproduction studies have not been conducted with (name of drug). It is also not known whether (name of drug) can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. (Name of drug) should be given to a pregnant woman only if clearly needed." The labeling must contain a description of any available data on the effect of the drug on the later growth, development, and functional maturation of the child.

(4) Pregnancy category D. If there is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, but the potential benefits from the use of the drug in pregnant women may be acceptable despite its potential risks (for example, if the drug is needed in a life-threatening situation or serious disease for which safer drugs cannot be used or are ineffective), the labeling must state: "Pregnancy Category D. See 'Warnings/Precautions' section." Under the "Warnings/Precautions" section, the labeling must state: (Name of drug) can cause fetal harm when administered to a pregnant woman. (Describe the human data and any pertinent animal data.) If this drug is administered to a woman with reproductive

potential, the patient should be apprised of the potential hazard to a fetus."

(5) Pregnancy category X. If studies in animals or humans have demonstrated fetal abnormalities or if there is positive evidence of fetal risk based on adverse reaction reports from investigational or marketing experience, or both, and the risk of the use of the drug in a pregnant woman clearly outweighs any possible benefit (for example, safer drugs or other forms of therapy are available), the labeling must state: "Pregnancy Category X. See 'Contraindications' section." Under "Contraindications," the labeling must state: "(Name of drug) may (can) cause fetal harm when administered to a pregnant woman. (Describe the human data and any pertinent animal data.) (Name of drug) is contraindicated in women who are or may become pregnant. If this drug is administered to a woman with reproductive potential, the patient should be apprised of the potential hazard to a fetus."

(B) Nonteratogenic effects. Under this subheading, the labeling must contain other information on the drug's effects on reproduction and the drug's use during pregnancy that is not required specifically by one of the pregnancy categories, if the information is relevant to the safe and effective use of the drug. Information required under this heading must include nonteratogenic effects in the fetus or newborn infant (for example, withdrawal symptoms or hypoglycemia) that may occur

because of a pregnant woman's chronic use of the drug for a preexisting condition or disease.

(ii) 7.2 Labor and delivery. If the drug has a recognized use during labor or delivery (vaginal or abdominal delivery), whether or not the use is stated in the indications section of the labeling, this subsection of the labeling must describe the available information about the effect of the drug on the mother and the fetus, on the duration of labor or delivery, on the possibility that forceps delivery or other intervention or resuscitation of the newborn will be necessary, and the effect of the drug on the later growth, development, and functional maturation of the child. If any information required under this subsection of the labeling is unknown, it must state that the information is unknown.

(iii) 7.3 Lactating women. (A) If a drug is absorbed systemically, this subsection of the labeling must contain, if known, information about excretion of the drug in human milk and effects on the nursing infant. Pertinent adverse effects observed in animal offspring must be described.

(B) If a drug is absorbed systemically and is known to be excreted in human milk, this subsection of the labeling must contain one of the following statements, as appropriate. If the drug is associated with clinically significant adverse reactions or if the drug has a known tumorigenic potential, the labeling must state: "Because of the potential for serious adverse

reactions in nursing infants from (name of drug) (or, "Because of the potential for tumorigenicity shown for (name of drug) in (animal or human) studies), a decision should be made whether to discontinue producing milk for consumption or to discontinue the drug, taking into account the importance of the drug to the lactating woman." If the drug is not associated with clinically significant adverse reactions and does not have a known tumorigenic potential, the labeling must state: "Caution should be exercised when (name of drug) is administered to a lactating woman."

(C) If a drug is absorbed systemically and information on excretion in human milk is unknown, this subsection of the labeling must contain one of the following statements, as appropriate. If the drug is associated with clinically significant adverse reactions or has a known tumorigenic potential, the labeling must state: "It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for clinically significant adverse reactions in nursing infants from (name of drug) (or, "Because of the potential for tumorigenicity shown for (name of drug) in (animal or human) studies), a decision should be made whether to discontinue producing milk for consumption or to discontinue the drug, taking into account the importance of the drug to the lactating woman." If the drug is not associated with clinically significant adverse reactions and

does not have a known tumorigenic potential, the labeling must state: "It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when (name of drug) is administered to a lactating woman."

(iv) 7.4 Pediatric use. (A) Pediatric population(s)/pediatric patient(s): For the purposes of paragraphs (c)(8)(iv)(B) through (c)(8)(iv)(H) of this section, the terms pediatric population(s) and pediatric patient(s) are defined as the pediatric age group, from birth to 16 years, including age groups often called neonates, infants, children, and adolescents.

(B) If there is a specific pediatric indication (i.e., an indication different from those approved for adults) that is supported by adequate and well-controlled studies in the pediatric population, it must be described under the "Indications and Usage" section of the labeling, and appropriate pediatric dosage information must be given under the "Dosage and Administration" section of the labeling. The "Pediatric use" subsection of the labeling must cite any limitations on the pediatric indication, need for specific monitoring, specific hazards associated with use of the drug in any subsets of the pediatric population (e.g., neonates), differences between pediatric and adult responses to the drug, and other information related to the safe and effective pediatric use of the drug.

Data summarized in this subsection of the labeling should be discussed in more detail, if appropriate, under the "Clinical Pharmacology" or "Clinical Studies" section. As appropriate, this information must also be contained in the "Contraindications," and/or "Warnings/Precautions" section(s) of the labeling.

(C) If there are specific statements on pediatric use of the drug for an indication also approved for adults that are based on adequate and well-controlled studies in the pediatric population, they must be summarized in the "Pediatric use" subsection of the labeling and discussed in more detail, if appropriate, under the "Clinical Pharmacology" and "Clinical Studies" sections. Appropriate pediatric dosage must be given under the "Dosage and Administration" section of the labeling. The "Pediatric use" subsection of the labeling must also cite any limitations on the pediatric use statement, need for specific monitoring, specific hazards associated with use of the drug in any subsets of the pediatric population (e.g., neonates), differences between pediatric and adult responses to the drug, and other information related to the safe and effective pediatric use of the drug. As appropriate, this information must also be contained in the "Contraindications," and/or "Warnings/Precautions" section(s) of the labeling.

(D) FDA may approve a drug for pediatric use based on adequate and well-controlled studies in adults, with other information supporting pediatric use. In such cases, the agency will have concluded that the course of the disease and the effects of the drug, both beneficial and adverse, are sufficiently similar in the pediatric and adult populations to permit extrapolation from the adult efficacy data to pediatric patients. The additional information supporting pediatric use must ordinarily include data on the pharmacokinetics of the drug in the pediatric population for determination of appropriate dosage. Other information, such as data from pharmacodynamic studies of the drug in the pediatric population, data from other studies supporting the safety or effectiveness of the drug in pediatric patients, pertinent premarketing or postmarketing studies or experience, may be necessary to show that the drug can be used safely and effectively in pediatric patients. When a drug is approved for pediatric use based on adequate and well-controlled studies in adults with other information supporting pediatric use, the "Pediatric use" subsection of the labeling must contain either the following statement, or a reasonable alternative:

> The safety and effectiveness of (drug name) have been established in the age groups __ to __ (note any limitations, e.g., no data for pediatric patients under 2, or only

applicable to certain indications approved in adults). Use of (drug name) in these age groups is supported by evidence from adequate and well-controlled studies of (drug name) in adults with additional data (insert wording that accurately describes the data submitted to support a finding of substantial evidence of effectiveness in the pediatric population).

Data summarized in the preceding prescribed statement in this subsection of the labeling must be discussed in more detail, if appropriate, under the "Clinical Pharmacology" or the "Clinical Studies" section of the labeling. For example, pediatric pharmacokinetic or pharmacodynamic studies and dose-response information should be described in the "Clinical Pharmacology" section of the labeling. Pediatric dosing instructions must be included in the "Dosage and Administration" section of the labeling. Any differences between pediatric and adult responses, need for specific monitoring, dosing adjustments, and any other information related to safe and effective use of the drug in pediatric patients must be cited briefly in the "Pediatric use" subsection of the labeling and, as appropriate, in the "Contraindications," "Warnings/Precautions," and "Dosage and Administration" sections.

(E) If the requirements for a finding of substantial evidence to support a pediatric indication or a pediatric use statement have not been met for a particular pediatric population, the "Pediatric use" subsection of the labeling must contain an appropriate statement such as "Safety and effectiveness in pediatric patients below the age of (__) have not been established." If use of the drug in this pediatric population is associated with a specific hazard, the hazard must be described in this subsection of the labeling, or, if appropriate, the hazard must be stated in the "Contraindications" or "Warnings/Precautions" section of the labeling and this subsection must refer to it.

(F) If the requirements for a finding of substantial evidence to support a pediatric indication or a pediatric use statement have not been met for any pediatric population, this subsection of the labeling must contain the following statement: "Safety and effectiveness in pediatric patients have not been established." If use of the drug in premature or neonatal infants, or other pediatric subgroups, is associated with a specific hazard, the hazard must be described in this subsection of the labeling, or, if appropriate, the hazard must be stated in the "Contraindications" or "Warnings/Precautions" section of the labeling and this subsection must refer to it.

(G) If the sponsor believes that none of the statements described in paragraphs (c)(8)(iv)(B) through (c)(8)(iv)(F) of

this section is appropriate or relevant to the labeling of a particular drug, the sponsor must provide reasons for omission of the statements and may propose alternative statement(s). FDA may permit use of an alternative statement if FDA determines that no statement described in those paragraphs is appropriate or relevant to the drug's labeling and that the alternative statement is accurate and appropriate.

(H) If the drug product contains one or more inactive ingredients that present an increased risk of toxic effects to neonates or other pediatric subgroups, a special note of this risk must be made, generally in the "Contraindications" or "Warnings/Precautions" section of the labeling.

(v) 7.5 Geriatric use. (A) A specific geriatric indication, if any, that is supported by adequate and well-controlled studies in the geriatric population must be described under the "Indications and Usage" section of the labeling, and appropriate geriatric dosage must be stated under the "Dosage and Administration" section of the labeling. The "Geriatric use" subsection of the labeling must cite any limitations on the geriatric indication, need for specific monitoring, specific hazards associated with the geriatric indication, and other information related to the safe and effective use of the drug in the geriatric population. Unless otherwise noted, information contained in the "Geriatric use" subsection of the labeling must pertain to use of the drug in persons 65 years of age and older.

Data summarized in this subsection of the labeling must be discussed in more detail, if appropriate, under "Clinical Pharmacology" or the "Clinical Studies" section of the labeling. As appropriate, this information must also be contained in the "Warnings/Precautions" or "Contraindications" section of the labeling.

(B) Specific statements on geriatric use of the drug for an indication approved for adults generally, as distinguished from a specific geriatric indication, must be contained in the "Geriatric use" subsection and must reflect all information available to the sponsor that is relevant to the appropriate use of the drug in elderly patients. This information includes detailed results from controlled studies that are available to the sponsor and pertinent information from well-documented studies obtained from a literature search. Controlled studies include those that are part of the marketing application and other relevant studies available to the sponsor that have not been previously submitted in the investigational new drug application, new drug application, biologics license application, or a supplement or amendment to one of these applications (e.g., postmarketing studies or adverse drug reaction reports). The "Geriatric use" subsection of the labeling must contain the following statement(s) or reasonable alternative, as applicable, taking into account available information:

(1) If clinical studies did not include sufficient numbers of subjects aged 65 and over to determine whether elderly subjects respond differently from younger subjects, and other reported clinical experience has not identified such differences, the "Geriatric use" subsection of the labeling must include the following statement:

> Clinical studies of (name of drug) did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

(2) If clinical studies (including studies that are part of marketing applications and other relevant studies available to the sponsor that have not been submitted in the sponsor's applications) included enough elderly subjects to make it likely that differences in safety or effectiveness between elderly and younger subjects would have been detected, but no such

differences (in safety or effectiveness) were observed, and other reported clinical experience has not identified such differences, the "Geriatric use" subsection of the labeling must contain the following statement:

> Of the total number of subjects in clinical studies of (name of drug), ____ percent were 65 and over, while ____ percent were 75 and over. (Alternatively, the labeling may state the total number of subjects included in the studies who were 65 and over and 75 and over.) No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

(3) If evidence from clinical studies and other reported clinical experience available to the sponsor indicates that use of the drug in elderly patients is associated with differences in safety or effectiveness, or requires specific monitoring or dosage adjustment, the "Geriatric use" subsection of the labeling must contain a brief description of observed differences or specific monitoring or dosage requirements and, as appropriate,

must refer to more detailed discussions in the "Contraindications," "Warnings/Precautions," "Dosage and Administration," or other sections of the labeling.

(C)(1) If specific pharmacokinetic or pharmacodynamic studies have been carried out in the elderly, they must be described briefly in the "Geriatric use" subsection of the labeling and in detail under the "Clinical Pharmacology" section of the labeling. The "Clinical Pharmacology" and "Drug interactions" section of the labelings ordinarily contain information on drug-disease and drug-drug interactions that is particularly relevant to the elderly, who are more likely to have concomitant illness and to use concomitant drugs.

(2) If a drug is known to be substantially excreted by the kidney, the "Geriatric use" subsection of the labeling must include the statement:

> This drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

(D) If use of the drug in the elderly appears to cause a specific hazard, the hazard must be described in the "Geriatric